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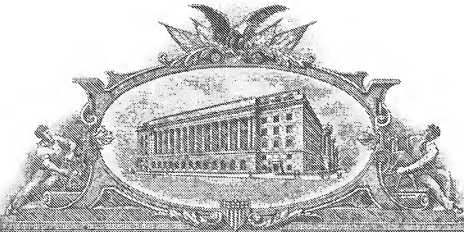
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COVER SHEET FOR PROVISIONAL APPLICATION FOR PATENT

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Sir:

This is a request for filing a PROVISIONAL APPLICATION under 37 CFR 1.53(c).

Docket Number		6750-209-888		Type a plus sign (+) inside this box 6	+
INVENTOR(s) APPLICANT(s)					
LAST NAME	FIRST NAME	MIDDLE INITIAL	RESIDENCE (CITY AND EITHER STATE OR FOREIGN COUNTRY)		
ABREU	Osvaldo		New Milford, New Jersey		
TITLE OF THE INVENTION (280 characters max)					
TAMPER RESISTANT DOSAGE FORM COMPRISING AN ADSORBENT AND AN ADVERSE AGENT					
JONES DAY CORRESPONDENCE ADDRESS :20583					
ENCLOSED APPLICATION PARTS (check all that apply)					
<input checked="" type="checkbox"/> Specification	Number of Pages	61	<input type="checkbox"/> Applicant claims small entity status, see 37 CFR §1.27		
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The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.
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Respectfully submitted,

Signature

James G. Markey
JONES DAY

REGISTRATION NO.
(if appropriate)

31,636

Date

3/30/04

☐ Additional inventors are being named on separately numbered sheets attached hereto.

Total number of cover sheet pages.

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PROVISIONAL APPLICATION FILING ONLY

**TAMPER RESISTANT DOSAGE FORM COMPRISING AN
ADSORBENT AND AN ADVERSE AGENT**

1. Field of the Invention

[0001] The present invention relates to pharmaceutical compositions and dosage forms comprising an adsorbent and an adverse agent, such as an opioid antagonist, which
5 are useful for preventing or discouraging tampering, abuse, misuse or diversion of a dosage form containing an active pharmaceutical agent, such as an opioid. The present invention also relates to methods for treating a patient with such a dosage form, as well as kits containing such a dosage form with instructions for using the dosage form to treat a patient. The present invention further relates to processes for preparing such
10 pharmaceutical compositions and dosage forms.

2. Background of the Invention

[0002] Considerable efforts have focused on the treatment or prevention of unintended or illicit use of a poison or a pharmaceutically active agent. For example, one treatment for a patient who ingests an excess of a drug or a poison involves
15 administration of an adsorbent such as activated charcoal (*see Remington's: The Science and Practice of Pharmacy* 1238 (20th ed. 2000)). The activated charcoal is intended to adsorb a portion of the drug or poison and prevent it from entering the circulatory system.

[0003] U.S. Patent No. 4,594,249 to Proctor *et al.* discloses a method for
20 alleviating the aftereffects of the consumption of alcoholic beverages by administration of activated charcoal to the alcohol consumer immediately before, during or immediately after alcohol consumption.

[0004] U.S. Patent No. 4,761,284 to Nishimura discloses a pharmaceutical composition comprising spherical particles of activated charcoal purportedly useful for
25 adsorbing exogenous or endogenous toxins in the gastrointestinal tract of a patient without disintegration of the pharmaceutical composition.

[0005] U.S. Patent Application Publication No. 2002/0155103 A1 discloses a composition comprising activated charcoal and limestone allegedly useful for preventing or delaying the onset of aftereffects associated with alcohol consumption.

[0006] There have also been attempts in the art to increase the tamper resistance of dosage forms, such as opioid analgesic dosage forms. Prior approaches to developing tamper resistant opioid dosage forms have included combining an opioid agonist with an opioid antagonist. Particular examples of such combinations include compositions including methadone and naloxone (U.S. Patent No. 3,773,955 to Pachter *et al.*); methadol or acetyl methadol and naloxone (U.S. Patent No. 3,966,940 to Pachter *et al.*); oxycodone and naloxone (U.S. Patent No. 4,457,933 to Gordon *et al.*); and buprenorphine and naloxone (U.S. Patent No. 4,582,835 to Lewis *et al.*).

[0007] U.S. Patent No. 6,228,863 to Palermo *et al.* discloses an oral dosage form which combines an opioid agonist and an opioid antagonist such that at least two separation steps are required to isolate the agonist.

[0008] U.S. Patent No. 5,610,193 to Al-Razzak *et al.* discloses a pharmaceutical composition comprising a pharmaceutically acceptable HIV protease inhibitor and solvent adsorbed onto a pharmaceutically acceptable adsorbent. The reference alleges that the composition provides improved oral bioavailability of the active compound that is poorly water soluble.

[0009] U.S. Patent No. 6,696,088 B2 to Oshlack *et al.*, and U.S. Patent Application Publication Nos. 2003/00073717 A1, 2003/0004177 A1 and 2003/0065002 A1 disclose oral dosage forms comprising an opioid agonist in releasable form and an opioid antagonist which is substantially not released when the dosage form is administered intact.

[0010] There remains a need in the art for improved tamper resistant dosage forms and improved techniques for their preparation.

3. Summary of the Invention

[0011] The present invention relates to pharmaceutical compositions and dosage forms comprising an adsorbent and an adverse agent. The present invention also relates

to methods for making such compositions and dosage forms. The present invention still further relates to methods for treating a patient with such pharmaceutical compositions or dosage forms, as well as kits comprising such pharmaceutical compositions or dosage forms and instructions directing the usage of the composition or dosage form to treat a patient. The dosage forms in accordance with the present invention include but are not limited to, oral dosage forms, including but not limited to, capsules or tablets; rectal suppositories; and vaginal suppositories. In certain embodiments, the dosage forms can comprise a plurality of particles.

[0012] In one embodiment, the invention relates to a dosage form comprising an adsorbent and an adverse agent. In another embodiment, the present invention relates to a dosage form comprising an active agent, an adsorbent, and an adverse agent.

[0013] In another embodiment, the invention relates to a dosage form comprising a plurality of first particles comprising an active agent; and a plurality of second particles comprising an adsorbent and an adverse agent, wherein at least a majority of the adverse agent is adsorbed on the adsorbent. In one embodiment, the invention relates to an oral dosage form comprising a plurality of first particles comprising an opioid agonist; and a plurality of second particles comprising an adsorbent and an opioid antagonist, wherein the first particles provide a controlled release of the opioid agonist upon oral administration to a patient.

[0014] In another embodiment, the invention relates to a dosage form comprising a core comprising an adsorbent and an adverse agent; and a shell comprising an active agent, wherein the shell at least partially covers or surrounds the core.

[0015] In one embodiment, at least a portion of the adverse agent is adsorbed onto at least a portion of the adsorbent. In another embodiment, at least a majority, *i.e.*, 50%, of the adverse agent is adsorbed onto at least a portion of the adsorbent. In a further embodiment, essentially all of the adverse agent is absorbed onto at least a portion of the adsorbent.

[0016] The compositions and dosage forms of the present invention can provide controlled release, immediate release or delayed release of the active agent and/or the adverse agent.

[0017] The invention also relates to methods for preparing a dosage form comprising an adsorbent and an adverse agent. In one embodiment, the invention relates to a method for preparing a dosage form comprising providing an adsorbent; providing a liquid comprising an adverse agent; contacting the adsorbent with the liquid comprising the adverse agent for sufficient time to allow at least a portion of the adverse agent to adsorb onto the adsorbent; separating the adsorbent from the liquid phase; and, optionally, washing the adsorbent.

[0018] In another embodiment, the invention relates to a method for preparing a dosage form comprising providing an adsorbent; providing a liquid comprising an adverse agent; adding the adsorbent to a fluidized bed; fluidizing the adsorbent; spraying the liquid onto the fluidized adsorbent; and, optionally, drying the adsorbent.

[0019] The invention also relates to a method of treating a condition, or a symptom thereof, comprising administering a dosage form of the invention comprising an adsorbent and an adverse agent to a patient. In one embodiment of the invention, the patient is treated for pain.

[0020] The present invention also relates to methods for reducing abuse, misuse or diversion of a dosage form for treating pain, which methods include administering to a patient in need thereof a dosage form of the invention.

[0021] In still another embodiment, the invention relates to a kit for treating a patient, including at least one dosage form of the invention and a set of instructions describing the use of the dosage form to treat the patient. In one embodiment of the invention, the kit is for treating a patient's pain.

[0022] The present invention can be understood more fully by reference to the following detailed description and examples, which are intended to exemplify non-limiting embodiments of the invention.

4. Brief Description of the Drawings

[0023] FIGS. 1a, 1b and 1c show perspective views of three embodiments of dosage forms of the invention.

[0024] FIG. 2 is a graph illustrating adsorption of naltrexone hydrochloride (in mg) onto activated charcoal as a function of time.

[0025] FIG. 3 is a graph illustrating the desorption of naltrexone hydrochloride (in ng/ml of wash solution) from activated charcoal as a function of the liters of wash solution.

[0026] FIG. 4 is a graph illustrating the desorption of naltrexone hydrochloride from activate charcoal (in mg) as a function of time during simulated *in vitro* dissolution test.

[0027] FIG. 5 is a comparative graph illustrating the desorption of naltrexone hydrochloride (in mg) as a function of time from a) sealed activated charcoal; and b) unsealed activated charcoal during simulated *in vitro* dissolution test.

5. Detailed Description of the Invention

5.1 Definitions

[0028] Any reference herein to any pharmaceutical agent, such as an active agent, an adverse agent, an opioid agonist or an opioid antagonist, shall, unless otherwise stated, includes any pharmaceutically acceptable form of such pharmaceutical agent, such as the free form, any pharmaceutically acceptable salt form, any pharmaceutically acceptable base form, any pharmaceutically acceptable hydrate, any pharmaceutically acceptable solvate, any stereoisomer, any optical isomer, as well as any prodrug of such pharmaceutical agent and any pharmaceutically active analog of such pharmaceutical agent, and mixtures of any two or more of the foregoing.

[0029] The phrase "pharmaceutically acceptable salt," as used herein, can be a salt formed from an acid and the basic group, such as a nitrogen group, of an active agent or an adverse agent. Generally, examples of such salts include, but are not limited, to sulfate, citrate, acetate, oxalate, chloride, bromide, iodide, nitrate, bisulfate, phosphate, acid phosphate, isonicotinate, lactate, salicylate, acid citrate, tartrate, oleate, tannate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucuronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, *p*-toluenesulfonate, glutubionate and palmoate (*i.e.*,

1,1'-methylene-bis-(2-hydroxy-3-naphthoate)) salts. The term "pharmaceutically acceptable salt" can alternatively be a salt prepared from an active agent or an adverse agent having an acidic functional group, such as a carboxylic acid or sulfonic acid functional group, and a pharmaceutically acceptable inorganic or organic base.

- 5 Generally, examples of such bases include, but are not limited to, hydroxides of alkali metals such as sodium, potassium, and lithium; hydroxides of alkaline earth metal such as calcium and magnesium; hydroxides of other metals, such as aluminum and zinc; ammonia, and organic amines, such as unsubstituted or hydroxy-substituted mono-, di-, or trialkylamines; dicyclohexylamine; tributyl amine; pyridine; N-methylamine, N-ethylamine; diethylamine; triethylamine; mono-, bis-, or tris-(2-hydroxy-lower alkyl amines), such as mono-, bis-, or tris-(2-hydroxyethyl)amine, 2-hydroxy-tert-butylamine, or tris-(hydroxymethyl)methylamine, N, N,-di-lower alkyl-N-(hydroxy lower alkyl)-amines, such as N, N,-dimethyl-N-(2-hydroxyethyl)amine, or tri-(2-hydroxyethyl)amine; N-methyl-D-glucamine; and amino acids such as arginine, lysine, and the like.
- 10

- 15 [0030] A "patient" or an "animal" is preferably a mammal, and includes, but is not limited to, a cow, monkey, horse, sheep, pig, chicken, turkey, quail, cat, dog, mouse, rat, rabbit, and guinea pig, and most preferably a human.

[0031] As used herein, the phrase "activated adsorbent" means an adsorbent that has undergone physical and/or chemical processing to increase its adsorptive capacity.

- 20 [0032] As used herein, the phrase "active agent" refers to a pharmaceutical agent that causes a biological effect when absorbed in sufficient amount into the blood stream of a patient.

[0033] As used herein, the phrase "adsorbent" refers to a pharmaceutically acceptable material exhibiting a large surface area and/or micropore volume capable of holding or retaining other molecules or substances onto its surface and/or pores and/or channels.

25

[0034] As used herein, the term "adsorbent/adverse agent" refers to an adsorbent which has adverse agent adsorbed onto at least a portion of its surface and/or pores and/or channels.

[0035] As used herein, the phrase “adverse agent” refers to a pharmaceutical agent that partially or completely negates or reverses at least one biological effect of an active agent present in the dosage form, *e.g.* euphoric effect, or produces one or more unpleasant physiological reactions, *e.g.*, vomiting, nausea, diarrhea, bad taste, when absorbed in sufficient amount into the blood stream of a patient or animal.

[0036] As used herein, the term “controlled release” refers to the *in vivo* release of an active agent from a dosage form in a controlled manner over an extended period of time. For example, a controlled release oral dosage form can release the drug, *e.g.*, over a 5 to 24 h interval.

10 [0037] As used herein, the phrase “delayed release” refers to an *in vivo* release process in which substantially no active agent is released from a dosage form for at least 1 h following administration. Once the delayed release occurs, the dosage form can release the active agent by a controlled release rate or by immediate release.

[0038] As used herein, the term “lamine” refers to a structure comprising more than one layer, *i.e.*, a multilayer structure.

[0039] As used herein, the phrase “opioid agonist” refers to an active agent which binds, optionally stereospecifically, to any one or more of several subspecies of opioid receptors and produces agonist activity.

20 [0040] As used herein, the phrase “opioid antagonist” refers to an adverse agent that either reduces, delays or reverses at least one biological effect of an opioid agonist, *e.g.*, euphoric effect, when absorbed in sufficient amount into the blood stream of a patient or animal.

5.2 Dosage Forms Comprising an Adsorbent and an Adverse Agent

25 [0041] The present invention is directed to pharmaceutical compositions and dosage forms comprising an adsorbent and an adverse agent, and to methods for making such compositions and dosage forms. In certain embodiments, the present invention relates to dosage forms comprising an active agent, an adsorbent and an adverse agent.

- [0042] In one embodiment, the invention relates to a dosage form comprising a plurality of first particles comprising an active agent; and a plurality of second particles comprising an adsorbent and an adverse agent, wherein at least a majority of the adverse agent is adsorbed on the adsorbent. In another embodiment, the invention relates to an oral dosage form comprising a plurality of first particles comprising an opioid agonist; and a plurality of second particles comprising an adsorbent and an opioid antagonist; wherein at least a majority of the adverse agent is adsorbed on the adsorbent, and wherein the first particles provide a controlled release of the opioid agonist upon oral administration to a patient.
- 10 [0043] In another embodiment, the invention relates to a dosage form comprising a core comprising an adsorbent and an adverse agent; and a shell comprising an active agent, wherein the shell at least partially covers or surrounds the core.
- [0044] The compositions and dosage forms of the present invention can provide any rate of release of the active agent, including, but not limited to, controlled release, immediate release or delayed release.
- 15 [0045] The present invention comprises at least one adsorbent/adverse agent. In certain embodiments, at least a portion of the adverse agent is adsorbed onto at least a portion of the adsorbent. In one embodiment, at least a majority, *i.e.*, at least 50%, of the adverse agent is adsorbed onto at least a portion of the adsorbent. In other embodiments, the percentage of the adverse agent which is adsorbed onto at least a portion of the adsorbent can be, *e.g.*, at 70%, at least 80%, or at least 90% or more. In one embodiment, essentially all of the adverse agent is adsorbed onto at least a portion of the adsorbent.
- 20 [0046] In certain embodiments, the compositions and dosage forms of the invention are formulated or made in a manner which reduces or prevents the *in vivo* release or absorption of the adverse agent into the blood stream following administration as intended of the intact dosage form to a patient. Thus, in certain embodiments, only a small amount, preferably less than about 10% by weight and more preferably less than about 1% by weight or none, of the adverse agent present in the dosage form is released
- 30 *in vivo* or absorbed into the blood stream following the administration as intended of an intact dosage form to a patient. In certain embodiments, when the adverse agent of the

adsorbent/adverse agent is an opioid antagonist, preferably less than about 0.5 mg, and more preferably less than about 0.05 mg, of the opioid antagonist is released *in vivo* following administration as intended of the intact dosage form to a patient.

[0047] In certain embodiments, the dosage form of the invention is designed to release a significant amount of the adverse agent *in vivo* if it is mistreated or misused. For example, an abuser may attempt to crush the dosage form in order to get a powder form of the composition, which form can be expected to provide an immediate release of active agent. In this case, crushing the formulation should expose the adverse agent present in the adverse agent/adsorbent, thereby allowing it to be released if administered. Alternatively, an abuser may attempt to dissolve the formulation in organic solvent, *e.g.*, ethanol, and isolate the active agent from solution. In this case, the extraction step with organic solvent should cause release a significant portion of the adverse agent, because the adverse agent will desorb or dissolve in the presence of a solvent such as ethanol.

[0048] In one embodiment, the adsorbent and adverse agent can be extruded with other materials such as binders, plasticizers, processing aids, excipients, or the like, or combinations of two or more of the foregoing.

[0049] In one embodiment, the present invention relates to solid dosage forms including a plurality of particles including an active agent, an adsorbent and an adverse agent, wherein the particles comprise a core comprising the adsorbent and the adverse agent and the core is at least partially surrounded by a shell comprising the active agent. The particles can be made by a process comprising co-extrusion of the core and the shell. Preferably, the shell surrounds a majority of the core component.

[0050] In certain embodiments, the adsorbent and the adverse agent can be present throughout the core. In one embodiment, the adsorbent and the adverse agent can be present in both the core and the shell. In another embodiment, the adsorbent and the adverse agent can be present in one or more inner layers of a multilayer particle.

[0051] In certain embodiments, the shell does not include any adsorbent/adverse agent. In other embodiments, the shell can include an adsorbent/adverse agent. In one embodiment, the amount of adverse agent present in the shell is less than the amount of adverse agent present in the core. In other embodiments, the shell can comprise an

adverse agent that is not an adsorbent/adverse agent, which adverse agent can have any release rate, including but not limited to, immediate release or controlled release.

5 [0052] In one embodiment, the adsorbent and the adverse agent are present only in the core, and the active agent is present only in the shell of a multilayer particle. In this embodiment, it is acceptable for small amounts of active agent and/or adverse agent to migrate to other components or layers following co-extrusion.

10 [0053] In one embodiment, the dosage forms of the invention can comprise one or more particles of any appropriate size. In one embodiment, the dosage form can comprise a plurality of small particles, such as, for example, particles having a size of from about 0.1 mm to about 5.0 mm in all dimensions, preferably from about 0.1 mm to about 3.0 mm in all dimensions. The particles can have any shape, such as cylindrical, spherical, square, ellipsoid, or any regular or irregular form, as desired.

15 [0054] In one embodiment, a dosage form is prepared to include an effective amount of melt-extruded multiparticulates ("MEMs") comprising an active agent within a hard or soft gelatin capsule. For example, a plurality of MEMs containing a core and a shell can be placed in a gelatin capsule in an amount sufficient to provide an effective sustained-release dose of the active agent when ingested and contacted by body fluid, without significant release of the adverse agent from the adsorbent/adverse agent. The particle size of the multiparticulates of the dosage form of the invention is preferably 20 from about 0.1 mm to about 5.0 mm in all dimensions and, more preferably, from about 0.1 mm to about 3.0 mm in all dimensions.

[0055] The dosage forms of the invention can be administered orally, such as in the form of a tablet or capsule; or rectally or vaginally, such as in the form of a suppository. In a preferred embodiment, the invention is directed to oral dosage forms.

25 [0056] In certain embodiments, the dosage forms are formulated to provide controlled release of the active agent *in vivo*, e.g., over about 5 to 8 h, preferably over at least 12 h, more preferably over at least 24 h, or longer.

30 [0057] When an intact dosage form including an active agent and an adsorbent/adverse agent is administered to a patient, only a small amount, and preferably almost none, of the adverse agent is released *in vivo*, whereas the active agent is released

- at the intended rate, which can vary from immediate release to controlled release. However, when a dosage form including an active agent, an adsorbent and an adverse agent is tampered with, *e.g.*, chewed, crushed, ground or dissolved, particularly in a solvent with heat (*e.g.*, greater than from about 45°C to about 50°C, up to about 100°C or
- 5 above), then the amount of adverse agent available for absorption into the body is substantially increased. The adverse agent is then available to exert its effect by either reducing at least one effect of the active agent, *e.g.*, euphoric effect, or eliciting one or more unpleasant effects in the patient. Thus, where the adverse agent is an antagonist of the active agent, at least one effect of the active agent is preferably substantially
- 10 diminished, or even eliminated, by the effect of the adverse agent. For example, where the active agent is an opioid agonist and the adverse agent is an opioid antagonist, an increased amount of opioid antagonist will become bioavailable when the dosage form is tampered with, interfering with opioid-receptor binding and reducing the opioid agonist's euphoric effect. Accordingly, only patients who take the dosage form of the present
- 15 invention as intended as an intact dosage form will experience substantially the full pharmacological effect of the active agent. Where the adverse agent is an emetic agent and the dosage form is tampered with, the release and absorption of the emetic agent will induce nausea and/or vomiting to discourage the user from tampering with the dosage form and also, in certain instances, to remove the active agent from the subject's body.
- 20 Abuse of the active agent in the dosage form will thus become less desirable because of the undesirable effects caused by the adverse agent.

- [0058] It is contemplated by the inventors that the release rate of the active agent and the adverse agent can be measured by *in vivo* methods or *in vitro* methods. However, the inventors do not represent that there is necessarily a direct correlation
- 25 between the results obtained via the two different methods.

- [0059] When administered as intended to a patient, the *in vivo* release of any adverse agent from the intact dosage form will preferably be sufficiently low so that it will not substantially reduce the benefits of the active agent or produce any unpleasant physiological reaction. The release rate of the adverse agent will be determined in large
- 30 part by the composition of the core, the sheath and the shell. The dosage form of the invention will typically release less than about 10% by weight of, preferably less than about 1% by weight of, more preferably substantially no adverse agent *in vivo* following

administration as intended of the intact dosage form. When the adverse agent is an opioid antagonist, the dosage form will preferably release less than about 0.5 mg, more preferably less than about 0.05 mg, of the opioid antagonist *in vivo* following administration as intended of the intact dosage form. For example, in one embodiment, 5 when the adverse agent is naltrexone opioid antagonist, preferably less than 0.0625 mg of naltrexone is released *in vivo* following administration of the intact dosage form as intended.

[0060] In certain embodiments, the dosage form preferably releases less than about 10% by weight, more preferably less than about 1% by weight, more preferably 10 substantially no adverse agent over a 36 h period during a standard *in vitro* dissolution test. For example, when the oral dosage form contains 5.0 mg of opioid antagonist and a dissolution test is conducted using the USP Basket Method (USP Type I basket, 100 rpm; 700ml simulated gastric filled, pH 1.2 without enzyme; 37°C for 1 h followed by 900ml simulated intestinal fluid; pH 7.5 without enzyme for the duration of the test), the 15 quantity of opioid antagonist released in simulated gastrointestinal fluid over 36 h can be less than 0.5 mg, and more preferably less than 0.05 mg.

[0061] In one embodiment of the invention, the solid dosage form can optionally be covered by a cosmetic coating. Any known type of cosmetic coating used for pharmaceutical dosage forms can be used so long as the dissolution pattern of the coated 20 dosage form achieves the intended purpose of the invention.

[0062] In certain embodiments, the dosage form can be cured by exposure to prolonged elevated temperatures in order to achieve increased stability. As used herein, the term “curing” means the heat treatment of the dosage form (or intermediate product) for purposes of obtaining a stabilized final dosage form. As understood by those skilled 25 in the art, when the formulations of the invention incorporate a polymer as part or all of the hydrophobic retarding agent, a heat treatment causes a curing effect and the polymer possibly cross-links with itself into a more stable state. When the formulations of the invention include a hydrophobic material such as, *e.g.*, hydrogenated vegetable oil or stearyl alcohol, the heat treatment can be more akin to an annealing of the formulation 30 rather than a curing of the polymer. However, for purposes of the present invention, the use of the term “curing” is deemed to encompass both curing and annealing. In situations where the hydrophobic material includes only a wax-like substance, curing can

be accomplished at a temperature from about 35°C to about 65°C, for a time period sufficient to achieve maximum stability, such as for a time period from about 5 to about 72 h. In other embodiments, curing is conducted at a temperature of from about 40°C to about 60°C, for a time period from about 5 to about 48 h or more, and preferably at least about 24 h. Suitable curing times that achieve the intended result of a stabilized dosage form can be determined by those of skill in the art.

5.3 Adsorbent Materials

[0063] Adsorbent materials useful for the present invention are water-insoluble, pharmaceutically acceptable materials that exhibit high surface area when measured by a method such as the Brunauer-Emmett-Teller (BET) model using nitrogen as the adsorptive (see Frederick S. Baker *et al.*, *Activated Carbon in 4 Kirk-Othmer Encyc. of Chem. Technol.* 1016 (4th ed. 1995)). Accordingly, in one embodiment, the adsorbent material suitable for use in the present invention exhibits a BET surface area of greater than 100 mg/g. Preferably, the adsorbent material exhibits a BET surface area of greater than 500 mg/g. Most preferably, the adsorbent material exhibits BET surface area of greater than 1000 mg/g.

[0064] Non-limiting examples of pharmaceutically acceptable adsorbent materials useful in the invention include one or more of high surface area forms of activated carbon including activated carbon charcoal and activated graphite; activated clays including kaolin, montmorillonite, attapulgite, illite, bentonite and halloysite; activated inorganic metal oxides and/or inorganic ion-exchange resins including silicon dioxide, colloidal silicon dioxide (e.g., CAB-O-SIL™, available from Cabot Corp.), and alumina; activated aluminum silicates and/or inorganic ion-exchange compositions such as zeolites; activated organic salts including organic ion-exchange resins such as polystyrene sulfonate; organic polymer-based adsorbents such as, e.g., microcrystalline cellulose, starch, maltodextrin, crospovidone (e.g., POLYPLAXDONE™ XL or XL10, available from GAF Corp.); and the like. Preferably, the adsorbent material is an activated adsorbent material. Activated adsorbent materials are commercially available and/or are activated by the user immediately prior to use by methods well-known in the art.

[0065] For example, methods of activating inorganic adsorbents generally involve removing surface adsorbed species such as, e.g., water, organic compounds and sulfides, using heat in combination with vacuum or an inert purge gas such as nitrogen.

[0066] Methods of activating inorganic ion-exchange compositions and organic ion-exchange resins generally involve treatment with a solution containing a specific salt, allowing an ion of the salt to adsorb onto the surface of the ion-exchange resin material, and, optionally drying the treated resin or material. The activated resin or material is then treated with the salt form of an adverse agent, the adverse agent ion displaces the pre-adsorbed ion, thereby affixing the adverse agent to the ion-exchange resin or material.

[0067] In one embodiment, the adsorbent material is selected from the group consisting of activated charcoal, alumina, bentonite and kaolin.

[0068] In a preferred embodiment, the adsorbent material is activated charcoal or activated carbon, both terms being used interchangeably herein to refer to a large surface area and/or micropore volume form of carbon containing low level of impurities (*see, e.g., The United States Pharmacopeia* 26 404 (2003)). Frederick S. Baker *et al.*, *Activated Carbon in Kirk-Othmer Encyc. of Chem. Technol.*, 1015-1022 (4th ed. 1995) discloses methods for preparing different grades of activated charcoal. Activated charcoal useful in the present invention exhibits a surface area of greater than about 100 m²/g. In certain embodiments, the surface area of the activated charcoal ranges from about 300 m²/g to about 2,000 m²/g.

[0069] The activated adsorbents useful in the present invention also exhibits high adsorptive capacity as measured by their adsorbance of the dye methylene blue ("MB value") from aqueous solution (*see* ASTM D3860-98 (adsorptive capacity of activated carbon) and ASTM C837-99 (adsorptive capacity of clay)). In one embodiment, the adsorbent material suitable for use in the present invention exhibits a MB value of greater than 30 mg/g; in another embodiment, the adsorbent material exhibits a MB value of greater than 150 mg/g; and in another embodiment, the adsorbent material exhibits a MB value of greater than 300 mg/g.

[0070] Non-limiting examples of adsorbent materials useful in the present invention include the activated charcoals listed below in Table 1.

Sample ^a	Feedstock material	Activation method	Physical form; typical use	Surface area, m ² /g			Pore volume, cm ³	
				BET ^b	external (t-plot)	MB ^c value	Micropores (t-plot)	mesopores (P/P8 = 0.95)
Calgon F-300 ^d	Coal	Steam	Pellets. Odor and color removal	901	63	105	0.38	0.10
Asbury #5597 ^e	Wood	Steam	Powder. Sugar production	907	147	183	0.36	0.22
B&S 207A ^f	Coal	Steam	Pellets. Food industry	977	63	125	0.42	0.09
Norit Darco KBB ^g	Wood	Chemical	Powder; color removal	1605	611	270	0.50	0.90
Pica PX714 ^h	Wood	Chemical	Pellets; odor removal	1730	502	300	0.58	0.69

^a N Cao *et al.*, *Energy & Fuels* 15:1263 (2001).

^b Surface area determined by the Brunauer-Emmet-Teller method by measuring the adsorption of N₂ at -196°C and CO₂ at 0°C onto the activated charcoal. See Brunauer, S. *et al.*, *J. Am. Chem. Soc.* 60:309 (1938).

^c ASTM D3860-98, "Standard Practice for Determination of Adsorptive Capacity of Activated Carbon by Aqueous Phase Isotherm Technique" using methylene blue.

^d Calgon Carbon Corp., Pittsburgh, PA.

^e Asbury Carbons, Inc., Asbury, NJ.

^f Barney & Sutcliffe Corporation, Columbus, OH.

^g NORIT Americas, Atlanta, GA.

^h PICA USA, Inc., Columbus, OH.

5.4 Hydrophobic Coating Materials

[0071] The dosage form can further comprise at least one hydrophobic coating material disposed on at least a portion of the surface of the adsorbent or

adsorbent/adverse agent. Without being limited by theory, it is believed that the hydrophobic coating material seals the pores and channels of the adsorbent material, thereby inhibiting or preventing any aqueous fluid, *e.g.*, a gastric fluid, from entering the pore or lattice structure of the adsorbent material. In one embodiment, the hydrophobic coating material covers at least a portion of the adsorbent/adverse agent.

[0072] In one embodiment, the at least one hydrophobic material is selected from the group consisting of acrylic and methacrylic acid polymers and copolymers, alkylcelluloses, natural and synthetic waxes, water insoluble waxes, fatty alcohols, fatty acids, hydrogenated fats, fatty acid esters, fatty acid glycerides, hydrocarbons, hydrophobic and hydrophilic polymers having hydrocarbon backbones, and mixtures of any two or more of the foregoing.

[0073] In one embodiment, the at least one hydrophobic coating material include, *e.g.*, esters of glycerol; fatty acids such as stearic acid and isostearic acid; alcohols such as stearyl alcohol, isostearyl alcohol, cetyl alcohol and cetostearyl alcohol; beeswax; hydrogenated castor oil, and hydrogenated cottonseed; and mixture thereof. In another embodiment, the hydrophobic coating material is stearyl alcohol.

5.5 Hydrophobic Matrix Materials

[0074] In certain embodiments, the dosage form and pharmaceutical compositions of the invention can further comprise a hydrophobic matrix material. The hydrophobic matrix material can be the same or different from the hydrophobic coating material. The hydrophobic matrix material can control, at least in part, the release characteristics of the active agent and the adverse agent; and can further prevent, inhibit or delay the release of the adverse agent. Hydrophobic matrix materials useful in the present invention include those that are known in the art to be insoluble or to have a low solubility in the gastrointestinal tract. Such materials include, but are not limited to, a hydrophobic material selected from the group consisting of acrylic and methacrylic acid polymers and copolymers, and alkylcelluloses. The matrix can also include additional hydrophobic materials such as zein, shellac, hydrogenated castor oil, hydrogenated vegetable oil or mixtures thereof

[0075] In one embodiment, the hydrophobic matrix material includes acrylic polymers. Examples of suitable acrylic polymers include, but are not limited to acrylic acid and methacrylic acid copolymers, methyl methacrylate copolymers, ethoxyethyl methacrylates, cyanoethyl methacrylates, aminoalkyl methacrylate copolymer, poly(acrylic acid), poly(methacrylic acid), methacrylic acid alkylamide copolymers, poly(methyl methacrylate), polymethacrylate, poly(methyl methacrylate) copolymer, poly(methacrylic acid) (anhydride), methyl methacrylate, polyacrylamide, aminoalkyl methacrylate copolymer, poly(methacrylic acid anhydride), and glycidyl methacrylate copolymers. Additional examples of suitable acrylic polymers include, but are not limited to, acrylic resins including copolymers synthesized from acrylic and methacrylic acid esters (e.g., the copolymer of acrylic acid lower alkyl ester and methacrylic acid lower alkyl ester) containing about 0.02 to 0.03 moles of a tri (lower alkyl) ammonium group per mole of acrylic and methacrylic monomer.

[0076] The acrylic polymer can comprise one or more ammonio methacrylate copolymers. Ammonio methacrylate copolymers are well known in the art, and are fully polymerized copolymers of acrylic and methacrylic acid esters with a low content of quaternary ammonium groups. In order to obtain a desirable dissolution profile for a given therapeutic agent, it might be necessary to incorporate two or more ammonio methacrylate copolymers having differing physical properties. For example, it is known

that by changing the molar ratio of the quaternary ammonium groups to neutral (meth)acrylic esters, the permeability properties of the resultant coating can be modified. One of ordinary skill in the art will readily be able to combine monomers to provide a copolymer that releases the therapeutic agent at the desired release rate. Copolymers of acrylate and methacrylate having a quaternary ammonium group functionality are commercially available as EUDRAGIT RS™ and EUDRAGIT RL™ (Röhm Pharma, GmbH, Weiterstat, Germany). Preferred ammonio methacrylate resins include EUDRAGIT RS™ in all forms, such as EUDRAGIT RS PO™. EUDRAGIT RS™ is known to be a water-insoluble copolymer of ethyl acrylate (EA), methyl methacrylate (MM) and trimethylammonium ethyl methacrylate chloride (TAM) in which the molar ratio of EA:MM:TAM is 1:2:0.01; see, e.g., U.S. Patent No. 6,306,391. EUDRAGIT RS PO™ is known to be a powdered form of EUDRAGIT RS™; see, e.g., U.S. Patent No. 5,492,692.

[0077] In one embodiment the hydrophobic matrix material includes a water insoluble cellulose polymer. In certain embodiments, the cellulose polymer is a cellulose ether, a cellulose ester, or a cellulose ester ether. Preferably, the cellulose polymers have a degree of substitution ("D.S.") on the anhydroglucose unit of from about zero up to and including about 3. As used herein the term D.S. means the average number of hydroxyl groups present on the anhydroglucose unit of the cellulose polymer that are replaced by a substituent group. Representative cellulose polymers include, but are not limited to, polymers selected from cellulose acrylate, cellulose diacrylate, cellulose triacrylate, cellulose acetate, cellulose diacetate, cellulose triacetate, mono-, di-, and tricellulose alkanylates, mono-, di-, and tricellulose arylates, and mono-, di-, and tricellulose alkenylates. Exemplary cellulose polymers include cellulose acetate having a D.S. of from about 1 to about 2 and cellulose acetate having a D.S. of from about 2 to about 3. Preferably, the cellulose polymer is ethylcellulose, cellulose acetate, cellulose propionate (low, medium, or high molecular weight), cellulose acetate propionate, cellulose acetate butyrate, cellulose acetate phthalate, or cellulose triacetate. A more preferred cellulose is ethylcellulose.

[0078] More specific cellulose polymers include cellulose propionate having a D.S. of about 1.8; cellulose acetate butyrate having a D.S. of about 1.8; cellulose triacrylate having a D.S. of about 2.9 to 3, such as cellulose triacetate, cellulose

trivalerate, cellulose trilaurate, cellulose tripalmitate, cellulose trisuccinate, and cellulose trioctanoate; cellulose diacylates having a D.S. of about 2.2 to 2.6 such as cellulose disuccinate, cellulose dipalmitate, cellulose dioctanoate, cellulose dipentanoate; and coesters of cellulose such as cellulose acetate butyrate, cellulose acetate octanoate butyrate, and cellulose acetate propionate.

[0079] In certain embodiments, the adsorbent/adverse agent can be intermixed with a hydrophobic matrix material. For example, a core comprising the adsorbent/adverse agent can further comprise up to about 50% by weight of one or more hydrophobic matrix materials, preferably up to about 50% by weight of the one or more hydrophobic matrix materials, more preferably up to about 25% by weight of the one or more hydrophobic matrix materials. The inclusion of a hydrophobic matrix material in the core can further reduce, delay or prevent the release or desorption of the adverse agent from the adsorbent material.

[0080] As noted above, the rate of release of active agent and the adverse agent is controlled, in part, by the composition of the hydrophobic matrix material. One of ordinary skill in the pharmaceutical arts can affect these release rates by varying the composition hydrophobic matrix material, such variations being determined by routine experimentation in view of the present disclosure.

5.6 Active Agent

[0081] Any kind of active agent can be used in the dosage forms of the present invention. Examples of useful active agents include, but are not limited to, analgesics, anti-inflammatory agents, anthelmintics, anti-arrhythmic agents, anti-bacterial agents, anti-viral agents, anti-coagulants, anti-depressants, anti-diabetics, anti-epileptics, anti-fungal agents, anti-gout agents, anti-hypertensive agents, anti-malarials, anti-migraine agents, anti-muscarinic agents, anti-neoplastic agents, erectile-dysfunction-improvement agents, immunosuppressants, anti-protozoal agents, anti-thyroid agents, anxiolytic agents, sedatives, hypnotics, neuroleptics, β -blockers, cardiac inotropic agents, corticosteroids, diuretics, anti-parkinsonian agents, gastrointestinal agents, histamine receptor antagonists, keratolytics, lipid regulating agents, anti-anginal agents, cox-2-inhibitors, leukotriene inhibitors, macrolides, muscle relaxants, nutritional agents, opioid analgesics, protease inhibitors, sex hormones,

stimulants, muscle relaxants, anti-osteoporosis agents, anti-obesity agents, cognition enhancers, anti-urinary incontinence agents, nutritional oils, anti-benign prostate hypertrophy agents, essential fatty acids, and non-essential fatty acids. The dosage forms can comprise more than one active agent.

- 5 **[0082]** More specific examples of active agents include, but are not limited to, opioids, benzodiazepines, barbiturates, and stimulants, such as methylphenidate and amphetamines, dronabinol, glutethimide, methylphenidate, nabilone, anabolic steroids, methylprylon, ethchlorovynol, ethinamate, fenfluramine, meprobamate, pemoline, levomethadyl, benzphetamine, chlorphentermine, diethylpropion, phentermine, 10 mebutamate, chlortermine, phenylacetone, dronabinol, nabilone, benphetamine, chloral hydrate, ethchlorovynol, paraldehyde, midazolam, and detropropoxyphene.

- [0083]** In certain embodiments, the active agent is an opioid agonist. Useful opioid agonists include, but are not limited to, alfentanil, allylprodine, alphaprodine, anileridine, benzylmorphine, bezitramide, buprenorphine, butorphanol, clonitazene, 15 codeine, desomorphine, dextromoramide, dezocine, diampromide, diamorphine, dihydrocodeine, dihydromorphine, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, eptazocine, ethoheptazine, ethylmethylthiambutene, ethylmorphine, etonitazene, etorphine, dihydroetorphine, fentanyl, hydrocodone, hydromorphone, hydromorphodone, hydroxypethidine, isomethadone, ketobemidone, 20 levorphanol, levophenacylmorphan, lofentanil, meperidine, meptazinol, metazocine, methadone, metopon, morphine, myrophine, narceine, nicomorphine, norlevorphanol, normethadone, nalorphine, nalbuphene, normorphine, norpipanone, opium, oxycodone, oxymorphone, pantopon, papaveretum, paregoric, pentazocine, phenadoxone, phendimetrazine, phendimetrazone, phenomorphane, phenazocine, phenoperidine, 25 piminodine, piritramide, propheptazine, promedol, properidine, propoxyphene, propylhexedrine, sufentanil, tilidine, tramadol, pharmaceutically acceptable salts thereof, and mixtures of any two or more of the foregoing.

- [0084]** In certain embodiments, the opioid agonist is selected from the group consisting of hydrocodone, morphine, hydromorphone, oxycodone, codeine, levorphanol, 30 meperidine, methadone, oxymorphone, buprenorphine, fentanyl and derivatives thereof, dipipanone, heroin, tramadol, etorphine, dihydroetorphine, butorphanol, levorphanol and

mixtures thereof. In one embodiment, the opioid agonist is oxycodone, hydromorphone or hydrocodone.

[0085] The term “benzodiazepines” refers to benzodiazepine and drugs that are derivatives of benzodiazepine and are able to depress the central nervous system.

- 5 Benzodiazepines include, but are not limited to, alprazolam, bromazepam, chlordiazepoxide, clorazepate, diazepam, estazolam, flurazepam, halazepam, ketazolam, lorazepam, nitrazepam, oxazepam, prazepam, quazepam, temazepam, triazolam, methylphenidate and mixtures of any two or more of the foregoing.

[0086] Barbiturates refer to sedative-hypnotic drugs derived from barbituric acid
10 (2, 4, 6-trioxohexahydropyrimidine). Barbiturates include, but are not limited to, amobarbital, aprobarbital, butabarbital, butalbital, methohexital, mephobarbital, metharbital, pentobarbital, phenobarbital, secobarbital and mixtures of any two or more of the foregoing.

[0087] Stimulants refer to drugs that stimulate the central nervous system.

- 15 Stimulants include, but are not limited to, amphetamines, such as amphetamine, dextroamphetamine resin complex, dextroamphetamine, methamphetamine, methylphenidate and mixtures of any two or more of the foregoing.

[0088] The active agent can be an agent intended for delivery to the colon, including, but not limited to, agents that act locally in the colonic region to treat a colon
20 diseases such as irritable bowel syndrome, irritable bowel disease, Crohn's disease, constipation, post operative atony, gastrointestinal infections, and therapeutic agents that deliver antigenic material to the lymphoid tissue. Active agents for the treatment of colon disease include, but are not limited to 5-ASA; steroids, such as hydrocortisone and budesonide; laxatives; stool softeners; octreotide; cisapride; anticholinergics; opioids;
25 calcium channel blockers; DNA for delivery to the cells of the colon; glucosamine; thromboxane A₂ synthetase inhibitors, such as Ridogrel; 5HT₃-antagonists, such as ondansetron; antibodies against infectious bacteria, such as *Clostridium difficile*; and antiviral agents, for example, for the prophylaxis of HIV.

[0089] Alternatively, the active agent can be an agent that is systemically active
30 and for which absorption is improved in the colon region. Such drugs include polar compounds such as: heparins; insulin; calcitonins; human growth hormone (HGH);

growth hormone releasing hormone (GHRH); interferons; somatostatin and analogues such as octreotide and vapreotide; erythropoietin (EPO); granulocyte colony stimulating factor (GCSF); parathyroid hormone (PTH); luteinising hormone releasing hormone (LHRH) and analogues thereof; atrial natriuretic factor (ANF); vasopressin;

5 desmopressin; calcitonin gene related peptide (CGRP); and analgesics.

[0090] The active agent particles can further comprise hydrophobic materials, binders, plasticizers, excipients, and combinations of any two or more of the foregoing. Suitable matrix materials include those which allow release of the active agent at a rate sufficient to achieve the desired result, *e.g.*, immediate release, sustained release or
10 delayed release. In one embodiment, a permeable matrix material is used, allowing for diffusive release of the active agent into the gastrointestinal fluid.

5.7 Adverse Agent

[0091] The adverse agent can be any pharmaceutical active agent which at least partially reduces or blocks the biological effect of an active agent or which creates an
15 unpleasant effect when absorbed into an animal's or patient's blood stream. Examples of adverse agents include, but are not limited to, antagonists of any therapeutically active agonist. When an opioid agonist is used as the active agent in the dosage form of the present invention, an opioid antagonist can be used as the adverse agent. Likewise, when a benzodiazepine is used as the active agent in the dosage form of the present invention, a
20 benzodiazepine antagonist can be used as the adverse agent. When a barbiturate is used as an active agent in the dosage form of the present invention, a barbiturate antagonist can be used as the adverse agent. When an amphetamine is used as an active agent in the dosage form of the present invention, an amphetamine antagonist can be used as the adverse agent. When the active agent is toxic when dosed above its normal therapeutic
25 range, *i.e.*, when there is a significant potential for an overdose, then an antidote of the toxic active agent can be used as the adverse agent.

[0092] In one embodiment, the adverse agent is an opioid antagonist. Opioid antagonists useful in the present invention include, but are not limited to, naloxone, naltrexone, nalmeferne, nalbuphine, nalorphine, cyclazacine, cyclazocine, levallorphan,
30 pharmaceutically acceptable salts thereof, and mixtures of any two or more of the foregoing.

[0093] Useful opioid antagonist salts include salts formed from an acid and the basic nitrogen group of an opioid antagonist. Examples of opioid antagonist salts include, but are not limited to, sulfate, citrate, acetate, oxalate, chloride, bromide, iodide, nitrate, bisulfate, phosphate, acid phosphate, isonicotinate, lactate, salicylate, acid citrate, tartrate, oleate, tannate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucaronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, *p*-toluenesulfonate, and palmoate (*i.e.*, 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)) salts.

[0094] Other opioid antagonist salts include salts prepared from an antagonist having an acidic functional group, such as a carboxylic acid or sulfonic acid functional group, and a pharmaceutically acceptable inorganic or organic base. Suitable bases include, but are not limited to those identified above in Section 5.1 in the paragraph which references the term "pharmaceutically acceptable salt".

[0095] In certain embodiments, the opioid antagonist is nalmefene, naloxone, naltrexone, or a pharmaceutically acceptable salt thereof. In another embodiment, the opioid antagonist is a naltrexone salt, such as naltrexone hydrochloride.

[0096] Benzodiazepine antagonists that can be used as the adverse agent of the present invention include, but are not limited to, flumazenil.

[0097] Barbiturate antagonists which can be used as the adverse agent of the present invention include, but are not limited to, amphetamines, as described herein.

[0098] Stimulant antagonists that can be used as the adverse agent of the present invention include, but are not limited to, benzodiazepines, described herein.

[0099] In another embodiment of the present invention, the adverse agent is an agent that causes an undesired physiological reaction, such as emesis. This type of adverse agent can be used with any kind of therapeutic agent including an opioid, a benzodiazepine, a barbiturate, or a stimulant. Examples of emetic agents suitable for use as the adverse agent in the present invention includes any drug that safely and effectively induces vomiting after administration including, but not limited to, ipecac and apomorphine.

5.8 Methods for Preparing the Dosage Form of the Invention

5.8.1 The Adsorbent/Adverse Agent

- [00100] In certain embodiments, the present invention relates to methods for preparing an adsorbent/adverse agent. For example, in some embodiments, the invention
- 5 relates to methods for adsorbing the adverse agent from a liquid phase onto the adsorbent material. In one embodiment, the invention relates to a method for preparing an adsorbent/adverse agent comprising: providing an adsorbent material; contacting the adsorbent material with a liquid phase comprising the adverse agent for sufficient time to allow at least a portion of the adverse agent to adsorb onto the adsorbent; separating the
- 10 adsorbent/adverse agent from the liquid phase; and, optionally, washing the adsorbent/adverse agent.

[00101] In one embodiment, the invention relates to methods for preparing a dosage form of the invention comprising extruding a composition comprising an adsorbent material and an adverse agent.

- 15 [00102] In another embodiment, the invention relates to methods for preparing a dosage form comprising a) co-extruding i) a core comprising an adsorbent and an adverse agent; and (ii) a sheath which at least partially surrounds the core and preferably surrounds a majority of the core, to form an extrudate strand; and b) cutting the extrudate strand to form a plurality of particles.
- 20 [00103] In another embodiment, the invention relates to methods for preparing a dosage form comprising a) co-extruding i) a core comprising an adsorbent and an adverse agent; ii) optionally, a sheath, which at least partially surrounds the core and preferably surrounds a majority of the core; and iii) a shell comprising an active agent, which at least partially surrounds the core and/or the optional sheath, to form an extrudate strand;
- 25 and b) cutting the extrudate strand to form a plurality of particles.

[00104] In another embodiment, the invention relates to methods for preparing a dosage form comprising a) forming a plurality of first particles comprising an active agent; b) co-extruding a plurality of second particles comprising i) a core comprising an adsorbent and an adverse agent; and ii) a sheath comprising a hydrophobic matrix

material which at least partially surrounds the core, and preferably surrounds a majority of the core; and c) adding the first and second particles to a dosage form.

5 [00105] In another embodiment, the invention relates to methods for making a dosage form comprising: a) co-extruding i) a core sheet comprising an adsorbent and an adverse agent; ii) optionally, a sheath, which at least partially surrounds the core, preferably which surrounds a majority of the core, more preferably which substantially or completely surrounds the core; and iii) a shell including an active agent, which at least partially surrounds the sheath, preferably which surrounds a majority of the sheath, more preferably which substantially or completely surrounds the sheath, to form a multilayer
10 extrudate sheet or laminate; and b) forming the multilayer extrudate sheet into dosage forms, such as tablets, caplets or a plurality of particles.

[00106] Adsorption (or sorption) processes and factors affecting the rate and extent of adsorption are well known in the art (*see, e.g., 16 Perry's Chemical Engineer's Handbook* 1-48 (6th ed. 1984); Douglas M. Ruthven, *Adsorption in 4 Kirk-Othmer Encyc. of Chem. Technol.* 493-528 (4th ed. 1995); and Stanley A. Gembricki *et al.*, *Adsorption, Liquid Separation in 4 Kirk-Othmer Encyc. of Chem. Technol.*, 573-600 (4th ed. 1995); the entire contents of each reference being expressly incorporated herein by reference).

20 [00107] In one embodiment, the adsorbance step is performed in a reaction vessel comprising the adsorbent and liquid phase, optionally with mixing. In another embodiment, the adsorbent is contained in a column and the liquid phase is circulated through the adsorbent material. The rate and/or extent of adsorption can be monitored by, *e.g.*, monitoring the change in concentration of the adverse agent in the liquid phase over time.

25 [00108] Suitable solvents for a process comprising adsorption from a liquid phase are those which can dissolve the adverse agent, but which will have a low tendency to redissolve the adverse agent once adsorbed onto the adsorbent material. Non-limiting examples of suitable solvents include water, aqueous solutions, such as Simulated Gastric Fluid (pH 1.2), Simulated Intestinal Fluid (pH 6.8), 0.1N hydrochloric acid solution and
30 0.1N phosphoric acid solution.

- [00109] In one embodiment, an aqueous solvent is used in the solution adsorption process having a pH ranging from about 1 to about 7. More preferably, the pH of the aqueous solvent ranges from about 1 to about 4. Most preferably, the pH of the aqueous solvent can be about 1.
- 5 [00110] In certain embodiments, the temperature of the liquid phase used in the solution adsorption process can be varied to affect the rate and extent of adsorption. One of ordinary skill in the art can determine the optimal reaction temperature by routine experimentation.
- [00111] The invention also relates to methods for preparing an adsorbent/adverse agent by a spraying a liquid phase comprising the adverse agent onto the adsorbent material. In one embodiment, the invention relates to a method for preparing an adsorbent/adverse agent comprising: providing an adsorbent material; providing a liquid phase comprising the adverse agent; adding the adsorbent material to a fluidized bed; fluidizing the adsorbent material; spraying the liquid phase onto the fluidized material; 15 and, optionally, drying the adsorbent/adverse agent. In one embodiment, the method of drying the sprayed particles is selected from the group consisting of forced air, reduced pressure, heat and mixtures of any two or more of the foregoing.
- [00112] The spray application process generally provides adsorbent that appears dry on the external surface, yet has internal surfaces that are "wet" with the liquid phase. 20 Depending on the solvating power of the solvent, the adverse agent may or may not be adsorbed onto the surface of adsorbent material. However, removal of the solvent by, e.g., reduced pressure evaporation, optionally with heat, causes the adverse agent to be deposited on the surface of the adsorbent material as the liquid vehicle is evaporated. The spraying process allows the use of solvents that would otherwise desorb the adverse agent. 25 agent.
- [00113] Non-limiting examples of solvents useful for the spray drying process include water as described above; alcohols including methanol, ethanol, n-propanol, i-propanol; dialkyl ethers including diethyl ether, di-propyl ether and d-butyl ether; and cyclic ethers such as tetrahydrofuran, and mixtures of any two or more of the foregoing.
- 30 [00114] In certain embodiments, the adsorbent/adverse agent further comprises a hydrophobic coating material. The coating material covers or seals the pores and

channels of the adsorbent/adverse agent, thereby further delaying, reducing or eliminating release of the adverse agent. The hydrophobic coating material can be applied using any conventional coating means provided the method of application does not cause significant desorption of the adverse agent from the adsorbent/adverse agent.

- 5 [00115] In one embodiment, the method for applying the hydrophobic coating material comprises: providing a liquid phase comprising a hydrophobic matrix material; and spraying the adsorbent/adverse agent with the liquid phase.

- [00116] In another embodiment, the method for applying the hydrophobic coating material comprises: providing a melt of the hydrophobic coating material; and applying
10 the melt to the adsorbent/adverse agent. In one embodiment, the hydrophobic coating material is applied to the adsorbent/adverse agent by dip-coating the solid into the melt.

- [00117] The invention also relates to methods for applying a hydrophobic coating material to the adsorbent/adverse agent during melt extrusion or granulation. In this embodiment, adsorbent/adverse agent and the hydrophobic coating material are added to
15 feed hopper together with other ingredients, and the mixture is extruded or compressed. Without being bound by theory, it is believed that energy required for the extrusion or compaction process is sufficient to cause the hydrophobic coating material to flow, and form a coating on the adsorbent/adverse agent.

- [00118] Additional details regarding formulation and manufacture of dosage forms
20 comprising an opioid agonist in releasable form and an opioid antagonist which is substantially not released are disclosed in U.S. Patent No. 6,696,088 B2 to Oshlack *et al.*, the entirety of which is expressly incorporated herein for all purposes.

5.8.2 Methods for Extruding or Co-Extruding the Dosage Form

- [00119] In certain embodiments, the present invention also relates to methods for
25 preparing a pharmaceutical composition or dosage form comprising an adsorbent/adverse agent by extruding, such as by melt extruding, a core comprising an adsorbent/adverse agent. In one embodiment, the core further comprises a hydrophobic material.

[00120] In one embodiment, the invention relates to methods for preparing a plurality of adsorbent/adverse agent particles by a) co-extruding a core comprising an

adsorbent/adverse agent, and a sheath which at least partially surrounds the core and preferably surrounds a majority of the core, to form extrudate strands; and b) cutting the extrudate strands to form a plurality of adsorbent/adverse agent particles. In one embodiment, the core comprises an adsorbent/adverse agent and a hydrophobic coating material, and the sheath comprises a hydrophobic matrix material.

5 [00121] In another embodiment, the invention relates to methods for preparing a dosage form comprising a) forming a plurality of first particles comprising an active agent; b) co-extruding a plurality of second particles comprising an adsorbent/adverse agent, and, optionally, a sheath comprising a hydrophobic matrix material, which at least partially surrounds the core, and preferably surrounds a majority of the core; and c) combining the first and second particles together.

[00122] In another embodiment, the invention relates to methods for making a dosage form by: a) co-extruding a core comprising an adsorbent/adverse agent; a sheath, which at least partially surrounds the core, preferably which surrounds a majority of the core, more preferably which substantially or completely surrounds the core; and a shell including an active agent, which at least partially surrounds the sheath, preferably which surrounds a majority of the sheath, more preferably which substantially or completely surrounds the sheath, to form to form extrudate strands; and b) cutting the extrudate strands to form a plurality of adsorbent/adverse agent particles.

20 [00123] In another embodiment, the invention relates to methods for making a dosage form by: a) co-extruding a core comprising an adsorbent/adverse agent; optionally, a sheath, which at least partially surrounds the core, preferably which surrounds a majority of the core, more preferably which substantially or completely surrounds the core; and a shell including an active agent, which at least partially surrounds the sheath, preferably which surrounds a majority of the sheath, more preferably which substantially or completely surrounds the sheath, to form a multilayer extrudate sheet or laminate; and b) forming the multilayer extrudate sheet into dosage forms, such as tablets, caplets or a plurality of particles. In one embodiment, the method comprises the use of a rolling punch to render the multilayer extrudate sheet into particles.

[00124] In certain embodiments, the extrudates are used in dosage forms such as tablets, caplets or a plurality of particles.

[00125] Generally, methods for preparing active agent-containing compositions or particles by extrusion and/or co-extrusion are well known. *See, e.g.*, U.S. Patent Nos. 5,958,452, 5,965,161 and 6,335,033, each of which is expressly incorporated herein in its entirety, which disclose known methods for extruding and forming pharmaceutical dosage forms, including dosage forms consisting of particles.

[00126] Co-extrusion methods to form two layer compositions or particles for administering an active agent are also known. *See, e.g.*, U.S. Patent Application Publication No. 2002/0119197 A1, which is expressly incorporated herein in its entirety for all purposes.

[00127] Methods for forming a dosage form of the invention by co-extrusion are discussed below. Unless otherwise stated, methods for preparing an extruded particle comprising only a core are similar to those for co-extrusion, except (1) only one hopper is used to feed the core formulation and (2) the die has only one orifice.

[00128] In one embodiment, a co-extrusion process is used to make pharmaceutical compositions or dosage forms comprising an adsorbent/adverse agent that releases the adverse agent in a limited amount *in vivo* following intact administration as intended to a patient. In one embodiment, the composition or dosage form comprises a co-extruded, adsorbent/adverse agent cylindrical particle having a core containing the adsorbent/adverse agent and which is at least partially radially surrounded along its length by a sheath that preferably does not contain any adverse agent. In a further embodiment, the co-extruded particles containing an adsorbent/adverse agent, such as an opioid antagonist, are placed in a gelatin capsule with particles containing an active agent.

[00129] The present invention further relates to methods for preparing a particulate adsorbent/adverse agent useful in a dosage form, comprising charging a core formulation comprising an adsorbent/adverse agent and, optionally, a hydrophobic coating material into a first extruder; charging a shell formulation comprising an active agent into a second extruder; heating the formulations in the first and second extruders; co-extruding

the formulations to form a strand comprising an adverse agent core radially surrounded by a shell comprising an active agent; and rendering the strand into particles.

[00130] In another embodiment, the invention relates to methods for forming a multi-layer dosage form comprising charging a core formulation comprising an adsorbent/adverse agent and, optionally, a hydrophobic coating material into a first extruder; charging a shell formulation comprising an active agent into a second extruder; heating the formulations in the first and second extruders; co-extruding the formulations to form a multilayer extrudate sheet or laminate; and b) forming the multilayer extrudate sheet into dosage forms, such as tablets, caplets or a plurality of particles. In one embodiment, the method comprises the use of a rolling punch to render the multilayer extrudate sheet into particles.

[00131] An example of an apparatus useful for the co-extrusion process of the present invention includes two powder-feeder hoppers, one for loading the adsorbent/adverse agent core components and one for loading the shell components. The adverse agent core components include the adsorbent/adverse agent; and, optionally, a hydrophobic coating material and additional materials including, but not limited to, additional retardants, binders, plasticizers and excipients, as described above. The shell components include the active agent, a controlled-release matrix material and additional materials including, but not limited to, additional retardants, binders, plasticizers and excipients as described below. The contents of each hopper are charged to an extruder. The outlet of each extruder is attached to the same coaxial die having multiple co-axial outlet orifices, thereby forming strands of extrudate with the adverse agent in the core of the strand and the shell radially surrounding the core.

[00132] Each extruder can, for example, be equipped with single or twin screws and heated barrels. Each screw extruder can, independently, be of the (i) counter-rotating (i.e., driven in opposite directions of rotation) non-intermeshing; (ii) co-rotating (i.e., driven in the same direction of rotation) non-intermeshing; (iii) counter-rotating intermeshing; or (iv) co-rotating intermeshing type. Each extruder can, independently, have a sole discharge port located at the end of its housing or a radial discharge port. Each screw extruder can, independently, have drive means at each end of the screw or a drive means present at only one end. Each screw extruder can, independently, have a length to diameter, or L/D, ratio of from 5-70, preferably from 20-60. Those in the art

are familiar with such apparatuses, *e.g.*, a Leistritz twin screw extruder having a vacuum attachment, a Leistritz Micro 18/GL 40D twin screw extruder, or a Warner & Pfleiderer model ZSK-30 twin screw extruder.

[00133] The temperature of each individually adjustable barrel zone of each
5 extruder is set to the required temperature for a given formulation, and the extruder is allowed to thermally equilibrate, typically for about 30 minutes. The inside pressure of the twin screw extruder can be maintained from about 600 to about 980 mbar negative.

[00134] After a steady state temperature is attained, the contents of each powder-
feeder hopper are fed into the separate pre-heated extruder, thereby forming in each
10 extruder an intimately mixed molten mass typically from about 30°C to about 200°C in temperature, preferably from about 50°C to about 150°C, through heating and mixing, as it is driven through a series of zones by intermeshing screws and kneading elements. Optionally, a vent port can be present in the extruder. If it is desired to add a liquid component, independently of any powdered formulation, to a molten mass, the liquid can
15 be injected into the extruder by any known means, for example, by an injection port supplied by a positive displacement pump, such as a gear pump.

[00135] The molten masses exiting each extruder are combined in a coaxial die, which is optionally downstream of a combining block and/or a main gate adaptor, then passed through the exit orifice of the die. In one embodiment, the extrudate is formed as
20 a single or multiple extruded strand(s) comprising an adverse agent core and a sheath which at least partially surrounds the core. In another embodiment, the extrudate is formed as a multi-layer sheet or laminate.

[00136] Generally, the rotation speed, in rpm, of each extruder is adjusted such that their combined output, at the die orifice, is from about 1 to about 20 kg/h or greater,
25 preferably from about 6 to about 8 kg/h. The rotation speed of each extruder is one of the parameters that can be adjusted so that the output of each extruder yields the desired ratio of the core to the sheath.

[00137] The dimensions and/or cross-sectional profile of the die exit orifice can be adjusted to vary the thickness and shape of the resulting strand or sheet. For example,
30 the orifice is not limited to a circular cross-sectional profile, but can be elliptical, square, rectangular, hexagonal, triangular, 5-pointed star-shaped, etc. In certain embodiments,

an orifice having a circular cross-section can be adjusted to provide a strand having a diameter from about 0.1 mm to about 5.0 mm. The shape of the strand is determined by, among other factors, the shape of the die exit orifice opening and the method of rendering the strand into particles.

- 5 **[00138]** The strand produced from the co-extrusion process is thereafter conveyed away from the orifice and solidified by methods known to those in the art, for example, using a fan-cooled tunnel or a continuous movable belt upon which the strand(s) congeal and harden upon cooling. The strand is directed to a suitable device to render the extruded strand into particles by methods known to those in the art, for example, using
- 10 laser cutting, a hot wire-cutter or a guillotine. Rendering the strand into particles can occur before, during or following congealing. In one embodiment, the hardened strand which results from the co-extrusion process is cut by a pelletizer, which can utilize rollers, a fixed knife, a rotating cutter and the like. The roller speed and cutter speed are set so as to produce particles of the desired size and release characteristics. Suitable
- 15 instruments and systems are available from distributors such as Rand Castle Inc. of New Jersey. Other suitable apparatus will be apparent to those of ordinary skill in the art.

- [00139]** In one embodiment, the co-extruded strand is cut to form a number of cylinders as shown in FIG. 1, where the adverse agent-containing core is exposed at both ends of the cylinder. In any case, the compositions of the adverse agent-containing core
- 20 and the sheath should be formulated accordingly to limit the rate of in vivo release of the adverse agent from the adsorbent/adverse agent.

- [00140]** Where a sheet is produced from the co-extrusion process, the sheet is processed as described above for the strand, except the extrudate is formed as a multi-layer sheet. The sheet can then be rendered into particles or tablets by any method, such
- 25 as using a rolling punch. Generally, methods for preparing compositions or particles by extrusion and/or co-extrusion are well known. *See, e.g.*, U.S. Patent Nos. 5,958,452, 5,965,161 and 6,335,033, each of which is expressly incorporated herein in its entirety, which disclose known methods for extruding and forming pharmaceutical dosage forms, including dosage forms consisting of particles.

- 30 **[00141]** In one embodiment, the co-extruded multilayer extrudate is cut, pinched, or crimped to form a number of particulates, such as, for example, those shown in FIG. 1,

where the adverse agent-containing core is substantially or completely enveloped by the sheath layer(s) and the shell layer(s). Advantageously, in a preferred embodiment, the action of a rolling punch device crimps or pinches the shell and sheath layers such that the sheath substantially or completely surrounds the core and the shell substantially or completely surrounds the sheath. In any case, the compositions of the core and the sheath should be formulated accordingly to limit or prevent the rate of *in vivo* release of the adverse agent from the adsorbent/adverse agent. Methods for forming extrudates into particles or tablets using devices such as a molding roll, a pinch device, a belt and a roller or tow rollers are disclosed in, for example, U.S. Patents No. 6,120,802 and 5,073,379).

10 [00142] In addition, it is to be understood that the particles can be any geometrical shape, such as a bead, a seed, a pellet, etc., depending upon the die exit orifice. In one embodiment, the particulates formed from strands will be spheroids with a diameter of from about 0.1 mm to about 3.0 mm. In another embodiment, the particulates formed from strands will be cylindrical with a length of from about 0.1 to about 3.0 mm and a diameter of from about 0.1 to about 3.0 mm.

[00143] When the particles are formed from a multilayer extrudate, the particles' shapes can further comprise modified cylindrical (e.g., having cylindrical sides with top and/or bottom curvature; having a substantially flat top and/or bottom with the sides having some degree of curvature, or a combination thereof), oval, elliptical, or the like, or some combination thereof, where "cylindrical" can include not only circular cross-sections but also one or more of the following cross-sections: triangular, square, rhomboidal, diamond, trapezoidal, pentagonal, hexagonal, octagonal, star-shaped (e.g., having 3, 4, 5, 6, or more points), or some combination thereof, including those shapes where the corners have been at least partially rounded. In one embodiment, the particulates formed can be ellipsoidal with dimensions (height, length, and width) from about 0.1 mm to about 3.0 mm. In another embodiment, the particulates formed can be cylindrical with similar dimensions.

[00144] Similarly, when the extrudate is a sheet, the dimensions and/or cross-sectional profile of the die orifice can be adjusted to vary the thickness and shape of the resulting multilayer sheet. For example, the die orifice is not limited to a rectangular cross-sectional profile, but can have a trapezoidal character (*i.e.*, where the width of the top of the extrudate is smaller than width of the bottom of the extrudate, or vice versa);

can have some degree of curvature associated with the width and/or thickness of the multilayer sheet or laminate (*i.e.*, top and/or bottom sides can have concave and/or convex curvature, such that the thickness changes across the width of the extrudate; in one embodiment, the die orifice opening has a very oblate oval shape); or can have any combination thereof. For example, an orifice having a circular cross-section can be adjusted to provide a multilayer sheet or laminate having a diameter from about 0.1 mm to about 50 mm, alternately from about 0.5 mm to about 20 mm, for example from about 1 mm to about 10 mm.

[00145] Following cutting, the co-extruded particles are collected and can be used in any manner for which such solid pharmaceutical composition is used. Optionally, following cutting, the particles are passed through a separator using #16 TBC (approximately 0.054") and #26 TBC (approximately 0.031") opening screens and collected. In a preferred embodiment, co-extruded particles containing an adverse agent and particles containing an active agent are placed together in hard gelatin capsules for oral dosage to patients

[00146] In one embodiment, the dosage form comprises a plurality of particles comprising a core, and, optionally, a shell which are placed in a gelatin capsule.

[00147] In one embodiment, the dosage form comprises a plurality of particles comprising a core, optionally, a sheath, and a shell which are placed in a gelatin capsule.

[00148] It will be apparent to one of ordinary skill in the art of pharmaceutical extrusion that the compositions and dimensions of the core, the optional sheath, and shell can be varied to achieve the desired release rate of the active agent. For example, by changing the co-extrusion die exit orifice dimensions, the thickness of the core, sheath and shell can be varied. In certain embodiments, the thickness of the core, the sheath and the shell can each be from about 0.05 mm to about 3.0 mm; in one embodiment, about 0.2 mm to about 1.0 mm. The desired thickness of the sheath can be determined, for example, by the dissolution rate of the hydrophobic matrix material and the thickness of the core. In certain embodiments, the thickness of the sheath is from about 0.05 mm to about 3.0 mm; in one embodiment, about 0.1 mm to about 1.0 mm. The thickness of the shell can be adjusted based upon, for example, the shell composition and desired rate of release of the active agent. In certain embodiments, the thickness of the shell can be

from about 0.05 mm to about 3.0 mm; in one embodiment, from about 0.1 mm to about 1.0 mm. In certain embodiments the thickness of the core, the optional sheath and the shell can be adjusted to provide a particle with a maximum dimension of about 5.0 mm or less; in one embodiment, about 3.0 mm or less.

- 5 **[00149]** In one embodiment, the dosage form comprises a plurality of MEM's. Optionally, following cutting and/or punching, the particles can be passed through a separator, for example, using #16 TBC (approximately 0.054") and #26 TBC (approximately 0.031") opening screens, and collected. In one embodiment, the particles are placed in hard or soft gelatin capsules for oral dosage to patients.
- 10 **[00150]** FIGS. 1a, 1b and 1c illustrate perspective views of three embodiments of a co-extruded particle or tablet of the present invention. In each of FIGS. 1a, 1b and 1c, core 3 comprises an adverse agent and a hydrophobic material. In FIG. 1a, sheath 2, which comprises a hydrophobic material, completely covers and surrounds core 3. Shell 1 comprises an active agent and a hydrophobic material, and completely covers and
- 15 surrounds sheath 2.

- [00151]** In the embodiment shown in FIG. 1b, the sheath 2 comprises upper sheath component 2a and lower sheath component 2b. The sheath 2 surrounds the top and the bottom portions of core 3, but leaves a small amount of core 3 exposed along the side of the particle. Similarly, the shell 1 comprises uppers shell component 1a and lower shell
- 20 component 1b. Shell 1 surrounds the top and the bottom of the sheath 2 while leaving a small portion of the sheath 2 and/or the core 3 exposed along the side of the particle.

- [00152]** In FIG. 1c, the sheath 2 comprises upper sheath component 2a and lower sheath component 2b which surround the top and the bottom of core 3 while leaving a small portion of core 3 exposed along the side. In this embodiment, the shell 1
- 25 completely covers and surrounds both sheath 2 and core 3.

- [00153]** In certain embodiments, the adsorbent/adverse agent is present in the core of an extruded particle or a co-extruded, multi-layer particle. The core containing the adsorbent/adverse agent can optionally comprise one or more binders, additional retardants, plasticizers, and/or excipients. Binders are useful for maintaining the integrity
- 30 of the matrix and can also help to prevent, inhibit or delay the release of an adverse agent into the bodily fluid. Examples of binders include natural and synthetic waxes, water

insoluble waxes, fatty alcohols such as stearyl alcohol, fatty acids such as stearic acid, hydrogenated fats, fatty acid esters, fatty acid glycerides, hydrocarbons, and hydrophobic and hydrophilic polymers having hydrocarbon backbones, water soluble polymers such as hydroxycelluloses, and mixtures of any two or more of the foregoing.

- 5 [00154] Plasticizers are useful when the hydrophobic matrix material contains cellulose polymer or an acrylic polymer. Non-limiting examples of suitable plasticizers include, *e.g.*, acetyl triethyl citrate and/or acetyl tributyl citrate.

- [00155] The adsorbent/adverse agent-containing core can also include other excipients, which can be added to improve the processability of the formulation during
10 extrusion and/or to improve the properties of the final product. Non-limiting examples of liquid excipients include water and oils, including those of petroleum, animal, vegetable, or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil, castor oil, triglycerides and the like. Examples of solid excipients include magnesium stearate, saline, gum acacia, gelatin, starch paste, talc, keratin, colloidal silica, urea and the like.
15 Coloring agents can also be added to the core. The excipient can be the same or different from the adsorbent materials.

[00156] In certain embodiments, the core can comprise one or more of the materials disclosed in Section 5.8.2.1 with respect to the sheath of the dosage form of the present invention.

20 5.8.2.1 Sheath

- [00157] In certain embodiments, the dosage form of the present invention can include a sheath which at least partially surrounds the core containing the adsorbent/adverse agent, and preferably surrounds a majority of the core containing the adsorbent/adverse agent. In certain embodiments, the sheath preferably includes a
25 hydrophobic matrix material and, optionally, binders, additional retardants, plasticizers and excipients. While, in certain embodiments, the sheath can contain a small percentage of adverse agent and/or active agent, it is preferred that the sheath does not contain any adverse agent or active agent.

- [00158] In one embodiment, the hydrophobic matrix material of the sheath
30 includes one or more materials selected from the group consisting of acrylic and

methacrylic acid polymers and copolymers, and water insoluble alkylcelluloses as described above hydrophobic coating material. The sheath can optionally comprise one or more additional hydrophobic materials, such as shellac, zein, hydrogenated castor oil, hydrogenated vegetable oil and mixtures thereof, as described above for the core.

5 [00159] The hydrophobic matrix material used in the sheath may or may not be the same as that optionally used as a hydrophobic coating material. Although the hydrophobic material used in the sheath will preferably be substantially insoluble in the gastrointestinal tract, this material could dissolve or biodegrade *in vivo* to some limited extent over time, thereby permitting the *in vivo* release from the core of a small amount
10 of adverse agent from the adsorbent material. One of ordinary skill in the pharmaceutical arts can alter the rate of such release, for example, by altering the composition of the sheath, increasing the thickness of the sheath, surrounding a larger portion of the core with the sheath, varying the size and/or dimensions of the core and/or varying the composition of the sheath and/or core. These and other methods will be known to one of
15 ordinary skill in the art or can be determined by routine experimentation in view of this disclosure.

[00160] In certain embodiments, the sheath can comprise from about 10% to about 99% by weight, preferably from about 40% to about 95% by weight, and more preferably from about 60% to about 90% by weight of the one or more hydrophobic matrix
20 materials.

[00161] The sheath can further comprise one or more additional retardants or one or more binders or plasticizers or excipients, or some combination thereof, such as those described in Section 5.8.2 for the adverse agent-containing core.

5.8.2.2 Shell

25 [00162] In certain embodiments, the dosage form of the present invention can include a shell comprising an active agent. The dosage form can provide any rate of release of the active agent *in vivo* from the shell following administration, such as immediate release, controlled release or delayed release. In certain embodiments, the dosage form provides a controlled release of the active agent, such as an opioid agonist.
30 Formulations and methods of manufacture of controlled release dosage forms of opioid agonists are known in the art. For example, U.S. Patents No. 5,958,452; 5,965,161;

5,968,551; 6,294,195 and 6,335,033, each of which is expressly incorporated herein by reference in its entirety for all purposes, disclose controlled release opioid agonist dosage forms. The disclosure of one or more of such patents includes details such as formulations, hydrophobic matrix materials, retardants, binders, plasticizers, and excipients, as well as extrusion methods for forming tablets, caplets and capsules containing MEMs, for controlled release opioid agonist dosage forms.

[00163] In certain embodiments, the active agent can be dispersed in a matrix which provides controlled release of the active agent *in vivo* following oral administration. Any suitable controlled-release matrix can be used to make the pharmaceutical compositions or dosage forms. Certain controlled-release matrices are known for oral formulations (*see, e.g.,* Lee et al., *Controlled-Release Drug-Delivery Systems, in Remington's: The Science and Practice of Pharmacy* 903-929 (20th ed. 2000), the disclosure of which is expressly incorporated herein in its entirety for all purposes). In addition to the controlled release dosage forms disclosed in the above-identified patents and publications, other examples of useful controlled-release matrices are described in U.S. Patent Nos. 6,143,328; 5,266,331; 5,549,912; 5,508,042; 5,656,295; 5,324,351; 5,356,467; and 5,472,712; the contents of which are each expressly incorporated herein by reference in its entirety for all purposes.

[00164] The controlled-release matrix can include fusible hydrophobic material(s), optionally combined with hydrophilic material(s). The hydrophobic fusible material(s) can be, for example, a hydrophobic polymer or a natural or synthetic wax or oil, such as hydrogenated vegetable oil or hydrogenated castor oil, which can, for example, have a melting point of from about 45°C to about 100°C, and in one embodiment from about 50°C to about 90°C. The hydrophobic material can be the same as that used as the hydrophobic coating material. The hydrophilic material can be a hydrophilic polymer such as a hydroxycellulose; a water soluble fusible material, such as polyethylene glycol; a water soluble particulate material such as lactose; or a slightly water soluble particulate material such as dicalcium phosphate.

[00165] While any known co-extrusion method can be used to make controlled release dosage forms according to the present invention, the preferred method is melt co-extrusion of the ingredients with suitable matrix materials. For example, the shell comprising an active agent dispersed in a controlled-release matrix can be prepared by,

e.g., extruding the active agent with a suitable non-fusible material including, but are not limited to, one or more of the following:

[00166] (a) Hydrophilic or hydrophobic polymers, such as gums, cellulose ethers, protein-derived materials, nylon, acrylic resins, polylactic acid, polyvinylchloride, starches, polyvinylpyrrolidones, and cellulose acetate phthalate. Of these polymers, cellulose ethers, for example, substituted cellulose ethers such as alkylcelluloses (*e.g.*, ethylcellulose), C₁ - C₆ hydroxyalkylcelluloses (*e.g.*, hydroxypropylcellulose and hydroxyethyl cellulose), and acrylic resins (*e.g.*, methacrylates such as methacrylic acid copolymers) can be used. The controlled-release matrix can conveniently contain from about 1% to about 80% (by weight) of the hydrophobic and/or hydrophilic polymer.

[00167] (b) Digestible, long chain (C₈ - C₅₀, in one embodiment C₈ - C₄₀) substituted or unsubstituted hydrocarbons, such as fatty acids; hydrogenated vegetable oils; fatty alcohols, such as lauryl, myristyl, stearyl, cetyl or, in one embodiment cetostearyl alcohol; glyceryl esters of fatty acids, for example, glyceryl monostearate; mineral oils; and waxes, such as beeswax, glycowax, castor wax, and carnauba wax. Hydrocarbons having a melting point of from about 25°C to about 90°C are used in one embodiment. Of these long chain hydrocarbon materials, fatty (aliphatic) alcohols are useful in one embodiment. The controlled-release matrix can contain up to about 60% (by weight) of at least one digestible, long chain hydrocarbon.

[00168] (c) Polyalkylene glycols. The controlled-release matrix can contain up to about 60% (by weight) of at least one polyalkylene glycol.

[00169] In one embodiment, a suitable controlled-release matrix for use in the dosage form of the invention can include one or more cellulose ethers or acrylic resins, or one or more C₁₂ - C₃₆ aliphatic alcohols; in another embodiment, C₁₂ - C₂₂, aliphatic alcohols and/or one or more hydrogenated vegetable oils. In one embodiment, a particularly suitable matrix includes one or more alkylcelluloses, or one or more C₁₂ - C₃₆ aliphatic alcohols; in another embodiment, C₁₂ - C₂₂, aliphatic alcohols and, optionally, one or more polyalkylene glycols. In another embodiment, the matrix contains from about 0.5% to about 60% by weight, and in another embodiment, from about 1% to about 50% by weight of the cellulose ether.

[00170] The acrylic resin can be, for example, a methacrylate such as methacrylic acid copolymer USNF Type A (EUDRAGIT L™), Type B (EUDRAGIT S™), Type C (EUDRAGIT L 100-55™), EUDRAGIT NE 30 D™, EUDRAGIT E™, EUDRAGIT RL™, or EUDRAGIT RS™ (commercially available from Röhm Pharma GmbH,

- 5 Weiterstat, Germany). In one embodiment, the matrix contains from about 0.5% to about 95% by weight of acrylic resin, and in another embodiment from about 10% to about 50% by weight of acrylic resin.

[00171] In the absence of polyalkylene glycol, the matrix in one embodiment contains from about 1% to about 40% by weight, in another embodiment from about 2%
10 to about 36% by weight of the aliphatic alcohol. When polyalkylene glycol is present in the oral dosage form, then the combined weight of the aliphatic alcohol and the polyalkylene glycol in one embodiment constitutes from about 2% to about 40% by weight, in another embodiment from about 2 to about 36% by weight of the matrix.

[00172] The polyalkylene glycol can be, for example, polypropylene glycol or, in
15 one embodiment, polyethylene glycol. The number average molecular weight of the polyalkylene glycol is in one embodiment from about 200 to about 15,000 Daltons, and in another embodiment from about 400 to about 12,000 Daltons.

5.8.3 Methods for Preparing Tablet Formulations

[00173] As noted above, the invention also relates to a tablet or particles
20 comprising an adsorbent/adverse agent. Tablets comprising the adsorbent/adverse agent of the present invention can be prepared by conventional means (*see, e.g., Rudnic et al., Oral Dosage Forms, in Remington's: The Science and Practice of Pharmacy* 858-885 (20th ed. 2000)), the entire contents of which are expressly incorporated herein by reference). In one embodiment, the particles or tablets are prepared by granulating and
25 compressing a formulation comprising an active agent and the adsorbent/adverse agent.

[00174] In another embodiment, the tablets are prepared by compressing a plurality of first particles comprising an active agent; and a plurality of second particles comprising an adsorbent/adverse agent.

[00175] In another embodiment, the particles or tablets are prepared by a granulating and compressing a dosage form comprising a core comprising an adsorbent/adverse agent and a shell comprising an active agent; wherein the shell at least partially covers the core.

5 [00176] It is to be understood that the particles or tablets can be any geometrical shape such as, for example, spherical, oval, pellet, etc., and can vary in size in any dimension depending on the method of manufacture, the amount and type of active agent and adsorbent/adverse agent, and the targeted patient. In certain embodiments, the tablet of the invention has a dimension in any direction from about 5 mm to about 75 mm; in
10 another embodiment, the tablet has a dimension in any direction from about 5 mm to about 30 mm; and in another embodiment, the tablet has a dimension in any direction from about 5 mm to about 15 mm.

[00177] The particles or tablets of the invention can further comprise pharmaceutically acceptable hydrophobic coating materials as defined above in Section
15 5.8.2.1; excipients such as binding agents (*e.g.*, pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (*e.g.*, lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (*e.g.*, magnesium stearate, talc or silica); disintegrants (*e.g.*, potato starch or sodium starch glycolate); wetting agents (*e.g.*, sodium lauryl sulphate); and other additives or excipients or as is
20 well-known in the art. The tablets can be coated by methods well-known in the art provided such coating does not interfere with the intended use of the tablet. A non-limiting example of a coating process is spray coating. In one embodiment, the tablets are formed by dip coating.

[00178] Other methods for preparing tablets from melt-extruded compositions are
25 described above.

5.9 Methods for Administration

[00179] The present invention is also directed to methods for treating a condition in a patient including administering a dosage form of the present invention to a patient in need of said treatment. The dosage form, can be, for example, an oral dosage form, such
30 as a tablet or capsule, or a rectal or vaginal dosage form, such as a suppository. In one

embodiment, the condition is pain and the dosage form includes an opioid and an adsorbent/opioid antagonist. In certain embodiments, the dosage form is administered to a patient twice a day, and in other embodiments, once a day.

5.10 Amount per Dosage Unit

5 [00180] In the dosage form of the present invention, the amount of the active agent per dosage unit is that which is an effective amount for its particular indication and is independent of the amount of the adverse-effect agent. For example, if the therapeutic agent is an opioid agonist, the amount of the opioid agonist in the dosage form of the present invention is generally from about 1 mg to about 800 mg, in one embodiment
10 from about 5 mg to about 160 mg. One of ordinary skill in the art can readily determine, without undue experimentation, the amount of therapeutic agent needed for a particular indication.

[00181] The amount of the adverse agent in the dosage form of the present invention is such that the adverse agent can give the intended adverse effect if, when
15 tampered with, a substantial amount of the adverse agent is released immediately from the dosage form and absorbed into an animal's blood. When, upon tampering with the dosage form, the adverse agent is intended to reduce or eliminate one or more of the pharmacological effects of the active agent, such as euphoria, the amount of the adverse agent in the dosage form is at least sufficient to reduce or eliminate those effects of the
20 active agent when both agents are substantially or completely released from the dosage form and absorbed into an animal's blood after tampering has occurred.

[00182] For example, in one embodiment, when the adverse agent is an opioid antagonist, such as naltrexone or nalmeferne, the amount of the opioid antagonist present in a dosage form of the present invention can be from about 0.1 mg to about 50 mg or
25 more. The opioid antagonists cyclazocine and naltrexone, when administered orally, retain much of their efficacy with a long duration of action, approaching 24 h. Amounts of less than about 10 mg of these opioid antagonists are typically used in oral formulations of the invention.

[00183] When, upon tampering, the adverse agent is intended to cause an
30 undesired physiological reaction, such as emesis, the amount of the adverse agent in the

dosage form is at least sufficient to cause such effect upon release after tampering has occurred.

[00184] For safety reasons, the amount of the adverse agent present in the dosage form should not be harmful to humans even if it is all immediately released. One of ordinary skill in the art can readily determine, without undue experimentation, the amount of adverse agent needed to elicit the intended adverse effect without being harmful.

[00185] In certain embodiments of the present invention, the ratio of the therapeutic agent to the adverse agent in the dosage form can be from about 1:1 to about 50:1 by weight, in one embodiment from about 1:1 to about 20:1 by weight. In certain other embodiments, the ratio can be about 1:1 to about 10:1 by weight.

[00186] In non-limiting embodiments in which the opioid agonist is hydrocodone, the controlled release dosage forms can include analgesic doses from about 5 mg to about 80 mg of hydrocodone per dosage unit. In non-limiting embodiments where the opioid agonist is hydromorphone, it can be included in an amount from about 2 mg to about 64 mg hydromorphone hydrochloride per dosage unit. In non-limiting embodiments in which the opioid agonist is morphine, it can be present in the dosage form from about 2.5 mg to about 800 mg morphine per dosage unit. In non-limiting embodiments in which the opioid agonist is oxycodone, the dosage forms can include from about 2.5 mg to about 160 mg oxycodone, and in another embodiment from about 20 mg to about 30 mg oxycodone per dosage unit. Controlled-release oxycodone formulations are known in the art. In a non-limiting embodiment, the opioid agonist can be tramadol in an amount from about 25 mg to 800 mg tramadol per dosage unit. The dosage form can contain more than one opioid agonist, and the doses of each can be adjusted accordingly.

[00187] The term "unit dose" is defined for purposes of the present invention as the total amount of dosage form needed to administer a single desired dose of active agent (e.g., opioid agonist) to a patient.

5.11 Methods for Vaginal or Rectal Administration

[00188] As noted above, the present invention is also directed to administration of a dosage form comprising an active agent and an adsorbent/adverse agent, in the form of

a suppository for absorption through the vagina or rectum. When administered as a suppository, the composition preferably includes a suppository base material. Any suppository base material can be used provided it does not dissolve the particulates. For example, cocoa butter is a traditional suppository base material, which can be modified by the addition of waxes to raise its melting point slightly. One or more water-miscible suppository base materials, such as polyethylene glycols of various molecular weights, can be included. When administered as a suppository, the combined concentration of the first and second plurality of particles in the suppository formulation is, typically, from about 5.0% to about 80% by weight of the composition.

5.12 Kits

[00189] The present invention is also directed to a kit containing at least one dosage form of the invention. In one embodiment, the dosage form is present in a container, *e.g.*, a bottle or box. In another embodiment, the kit further includes a set of instructions directing the use of the dosage form to treat a patient, *e.g.*, for pain. In one embodiment, the instructions can be a printed label affixed to or printed on the container. In another embodiment, the instructions can include a printed sheet inserted into the container or into the packaging which contains the container. The instructions can also state that the dosage form and/or its usage are designed to reduce abuse, misuse or diversion of the dosage form.

[00190] All patents, applications, publications, test methods, literature, and other materials cited above are hereby incorporated herein by reference in their entirety for all purposes.

6. Examples

[00191] The following examples are set forth to assist in understanding the invention and should not be construed as specifically limiting the invention described and claimed herein. Such variations of the invention, including the substitution of all equivalents now known or later developed, which would be within the purview of those skilled in the art, and changes in formulation or minor changes in experimental design, are to be considered to fall within the scope of the present invention.

6.1 Example 1. Process for Preparing Charcoal/Naltrexone

[00192] Example 1 describes a non-limiting method for making an adsorbent/adverse agent. The adsorbent used was Darco™ activated charcoal obtained from EM Science, an affiliate of Merck KGaA of Darmstadt, Germany. The Darco™ activated charcoal used was 20 to 40 mesh black granular charcoal which passed the USP absorptive power test (*see The United States Pharmacopeia* 26 404 (2003)) for activated charcoal.

[00193] The activated charcoal (5.02g) was added to a solution of naltrexone hydrochloride (504.26 mg)(obtained from Mallinkrodt, St. Louis, MO in 0.1N HCl (900 ml). The resultant mixture was stirred at 100 RPM for 120 h at 37°C, and the adsorption (or uptake) of naltrexone hydrochloride into the activated charcoal was monitored by measuring the decrease in concentration of the drug in the liquid phase using high performance liquid chromatography (HPLC). The data was used to calculate the amount of naltrexone adsorbed onto the activated charcoal.

$$\text{adsorbed naltrexone} = (\text{naltrexone}_{(\text{initial})}) \times \left(1 - \frac{\text{HPLC peak area}_{(t=2 \text{ h})}}{\text{HPLC peak area}_{(t=0)}}\right)$$

$$\text{adsorbed naltrexone} = (504.26 \text{ mg}) \times \left(1 - \frac{215860}{483568}\right) = 279.16 \text{ mg}$$

[00196] The data are provided in Table 2 and plotted in FIG. 2.

Table 2. Adsorption of naltrexone hydrochloride onto activated charcoal from a 0.1N aqueous solution at 37°C as a function of time.

Time, min	Naltrexone content in fluid, HPLC area %	Naltrexone content in fluid, mg	Naltrexone adsorbed onto the activated charcoal, mg	Naltrexone adsorbed from solution, %
0	483568	504.26	0.00	0.00
10	370707	386.57	117.69	23.34
20	328801	342.87	161.39	32.01
30	301659	314.57	189.69	37.62
40	283574	295.71	208.55	41.36
50	264151	275.45	228.81	45.37
60	252683	263.50	240.76	47.75
70	246125	256.66	247.60	49.10
80	238100	248.29	255.97	50.76
90	227373	237.10	267.16	52.98
100	220620	230.06	274.20	54.38

120	215860	225.10	279.16	55.36
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[00197] The results show that substantially all of the naltrexone adsorption was completed within ~1.5 h. The mixture was vacuum filtered using a sintered glass frit. The resultant filter cake was maintained on the glass frit under dynamic vacuum to provide a charcoal adsorbent naltrexone adverse agent as a free-flowing powder ("Charcoal/Naltrexone"). Based on the data in FIG. 3, the calculated content of naltrexone hydrochloride in the Charcoal/Naltrexone at the end of reaction (t=2 h) was 5.56 w.%. 5

[00198] *Dynamic Desorption of the Charcoal/ Naltrexone:* The

Charcoal/Naltrexone from above was transferred to a 1-liter sintered glass filter funnel, and washed with 63 x 1 L of 0.1 N HCl. The concentration of naltrexone hydrochloride in the wash filtrates was measured using HPLC as described above. The results are provided in Table 3 and plotted in FIG. 3. 10

Table 3. Desorption of naltrexone hydrochloride from activated charcoal as a function of volume of added 0.1 N HCl at 25°C. 15

Volume of 0.1N HCl added, liters	Naltrexone HCl extracted, ng
1	7899.8
7	2231.4
10	2904.3
11	2124.4
12	2690.3
13	2238.1
14	1921.7
15	1770.5
19	1246.0
23	1160.1
27	1497.6
31	996.9
35	742.6
39	651.7
43	566.1
47	467.2
51	492.4
55	442.6
59	426.8
63	383.4

[00199] The results show that the majority of the desorption of naltrexone hydrochloride occurred during the about the first 18 wash steps.

[00200] After the last wash, the resultant cake was dried on the filter flask to provide a dry free-flowing solid form of the acid-washed Charcoal/Naltrexone ("Acid-Washed Charcoal/Naltrexone"). The naltrexone hydrochloride content in the Acid-Washed Charcoal/Naltrexone was determined by grinding a portion of the solid to a fine powder using a mortar and pestle followed by methanol extraction as follows. A weighed portion of the ground Acid-Washed Charcoal/Naltrexone (~50mg) was added to a 100ml volumetric flask, 50ml of methanol was added, and the resultant mixture was sonicated for 15 minutes at room temperature. The mixture was allowed to cool to room temperature. A 4.000 ml aliquot was removed via pipette, transferred to a 250 ml volumetric flask, and diluted to 250.00 ml with 0.1 N HCl. The diluted mixture was shaken at 25°C for 15-30 minutes, and the resultant cloudy liquid was filtered through Whatman HX nylon filter paper. The concentration of naltrexone in the filtrate was then determined using HPLC against a naltrexone standard. The mean naltrexone content (n=3 samples of ground Acid-Washed Charcoal/ Naltrexone) was 3.06wt.%.

[00201] *Static Desorption of the Acid-washed Charcoal/ Naltrexone:* A portion of the Acid-Washed Charcoal/Naltrexone from above (~50 mg) was added to a 2000 ml beaker equipped with a paddle containing 900ml of 0.1N HCl at a temperature of 37°C. The contents of the beaker were mixed at 100 RPM for 72 h, and the naltrexone concentration in the liquid phase was monitored using HPLC. The data obtained in the static desorption study were normalized to the theoretical concentration of naltrexone if all the drug desorbed. The data are provided in Table 4 and plotted in FIG. 4, each point corresponding to the mean of n=6 samples of Acid-Washed Charcoal/Naltrexone samples.

Table 4. Desorption of naltrexone hydrochloride from activated charcoal as a function of time during in a simulated *in vitro* dissolution test.

Time, h	Naltrexone desorbed, mg	Naltrexone desorbed (dissolved), %	Naltrexone remaining adsorbed on the activated charcoal, mg	Naltrexone remaining adsorbed on the activated charcoal, %
0	0	0	3.06	3.06
1	0.19	12.4	1.34	2.68
2	0.21	13.7	1.32	2.64
3	0.29	18.7	1.24	2.49
4	0.25	16.6	1.28	2.55
5	0.30	19.7	1.23	2.46
6	0.33	21.3	1.20	2.41
7	0.35	23.0	1.18	2.36
8	0.38	25.1	1.15	2.29
9	0.40	26.3	1.13	2.26
10	0.43	27.8	1.10	2.21
11	0.43	27.8	1.10	2.21
12	0.44	28.7	1.09	2.18
18	0.46	30.0	1.07	2.14
24	0.50	32.8	1.03	2.06
36	0.57	37.4	0.96	1.92
72	0.60	39.0	0.93	1.87

[00202] The results show that most, if not all, of the naltrexone desorbed within the first 36 h. Based on the content of naltrexone in the liquid phase after 72 h of static adsorption, the calculated content of naltrexone in the Acid Washed Charcoal/Naltrexone was 61% of its initial value (3.09 wt.%) or 1.9 wt.%. 5

[00203] The results of the above desorption studies show that an adsorbent/adverse agent such as Charcoal/Naltrexone is useful for preventing release of the adverse agent.

6.2 Example 2. Process for Preparing Charcoal/Naltrexone Sealed with a Hydrophobic Matrix Material

[00204] *Sealing the Charcoal/Naltrexone with a hydrophobic coating material:* A beaker containing stearyl alcohol (about 10-15 g) was placed on a hot plate, heat was applied to melt the alcohol, and the melt was further heated to a temperature of 67°C. A portion of the Charcoal/Naltrexone prepared in Example 1 above (200.41 mg) was added to a 100 mesh USP dissolution basket. The basket was fully immersed into the melt for 5-10 min and moved in an up and down reciprocating manner to aid in the coating of the Charcoal/Naltrexone. The basket was removed from the melt and allowed to cool to 10

ambient temperature to provide the sealed Charcoal/Naltrexone ("Sealed Charcoal/Naltrexone") (472.45 mg) as a black solid with a white shade. The content of naltrexone hydrochloride in the Sealed Charcoal/Naltrexone was calculated using the weight of Charcoal/Naltrexone starting material and its naltrexone content (3.06 wt.%)

5 together with the weight of the Sealed Charcoal/Naltrexone product.

$$[00205] \quad \text{naltrexone content} = (3.06 \text{ wt}\%) \times \frac{(\text{weight of Charcoal/Naltrexone})}{(\text{weight of Sealed Charcoal/Naltrexone})}$$

$$[00206] \quad \text{naltrexone content} = (3.06 \text{ wt}\%) \times \frac{(200.14 \text{ mg})}{(472.45 \text{ mg})} = 1.30 \text{ wt}\%$$

- 10 [00207] *Static Desorption of the Sealed Charcoal/Naltrexone:* A portion of the Sealed Charcoal/Naltrexone (~77 mg) was added to a 2000ml beaker equipped with a paddle containing 0.1N HCl (900 ml), and the contents were mixed at 100 RPM for 72 h at 37°C. The naltrexone concentration in the liquid phase was monitored using HPLC. The data obtained in the static desorption study are provided in Table 5 and plotted in
- 15 FIG. 5 (-o-o-o-), and represent the mean for n=6 samples of Sealed Charcoal/Naltrexone samples. For comparison, the same data were collected and plotted in FIG. 5 for the Charcoal/Naltrexone (-□-□-□-) prepared in Example 1 (n=6 samples).

Table 5. Desorption of naltrexone hydrochloride as a function of time from unsealed activated charcoal (charcoal/naltrexone) and activated charcoal sealed with stearyl

20 alcohol (sealed charcoal/naltrexone) during simulated *in vitro* dissolution test.

Time, h	Naltrexone desorbed from unsealed charcoal/naltrexone, mg	Naltrexone desorbed from sealed charcoal/naltrexone, mg,
1	192.054	23.494
2	157.087	24.027
3	272.241	26.714
4	227.314	26.799
5	294.844	31.508
6	333.870	28.384
7	375.422	37.240
8	420.648	28.247
9	449.391	27.687
10	484.948	26.549
11	444.769	31.781
12	471.184	27.838
18	471.023	31.393

24	516.712	33.809
36	569.693	35.227
72	609.872	42.137

- [00208] After mixing Charcoal/Naltrexone for 72 h, the concentration of naltrexone hydrochloride in the liquid phase was about 610 ng/ml. In contrast, after mixing the Sealed Charcoal/Naltrexone for 72 h, the concentration of naltrexone hydrochloride in the liquid phase was only about 42 ng/ml. The results show that sealing
- 5 Charcoal/Naltrexone with a suitable hydrophobic coating material can further prevent release of adverse agent from the adsorbent.

6.3 **Example 3. Process for Preparing Acid-Washed Charcoal/Naltrexone Sealed with a Hydrophobic Matrix Material**

- [00209] *Sealing the Acid-Washed Charcoal/ Naltrexone with a hydrophobic coating material:* The stearyl alcohol coating procedure described in Example 2 was repeated using the Acid-Washed Charcoal/Naltrexone prepared in Example 1. The content of naltrexone hydrochloride in the Sealed Acid-Washed Charcoal/Naltrexone (“Sealed Acid-Washed Charcoal/Naltrexone”) was calculated using the weight of the Acid-Washed Charcoal/Naltrexone starting material and its naltrexone content (3.06
- 10 wt.%) together with weight of Sealed Acid-Washed Charcoal/Naltrexone. The mean naltrexone hydrochloride content in the Sealed Acid-Washed Charcoal/Naltrexone product (based on n=6 samples of Acid-Washed Charcoal/Naltrexone) was 1.30 wt.%. 15

- [00210] *In Vitro Desorption of the Sealed Acid-Washed Charcoal/Naltrexone:* A portion of the Sealed Acid-Washed Charcoal/Naltrexone (~250mg) was added to a USP
- 20 type 2 dissolution vessel equipped with a paddle containing 900 ml of 0.1N HCl at 37°C, and the contents of the dissolution vessel were mixed at 100 RPM for 120 h. Analysis of the liquid phase (HPLC) showed that no detectable naltrexone was released over at least 120 h.

25 6.4 **Example 4: Release of Naltrexone from Sealed Acid-Washed Charcoal/Naltrexone upon Tampering**

- [00211] A sample of Sealed Acid-Washed Charcoal/Naltrexone from Example 3 was crushed using a mortar and pestle until a finely divided powder was formed. Weighed portions of the sample (~0.025g) were added to scintillation vials containing

10.00 ml of either deionized distilled water (pH 6.5) or 40% ethanol in water. The resultant mixtures were shaken by hand for 10 minutes at 25°C and at 100°C. The content of naltrexone in the liquid phases of the samples was then determined using HPLC against a known naltrexone standard, and the results are shown in Table 2 below.

- 5 Table 6 also includes comparative data for uncrushed Sealed Acid-Washed Charcoal/Naltrexone in water and methanol at 25°C.

Table 6. Results of naltrexone desorptive extraction from Sealed Acid-Washed Charcoal/Naltrexone in water and alcohols.

Sample preparation / extraction solvent / temperature	Sealed Acid-Washed Charcoal/Naltrexone, mg	Naltrexone released, mg
Uncrushed / water / 25°C	87.61	~0
Uncrushed/ methanol (neat) / 25°C	85.20	~0
Crushed / water / 25°C	97.41	0.00076
Crushed / 40% ethanol / 25°C	93.740	0.0092
Crushed / 40% ethanol / 100°C	118.14	0.04123

[00212] The results of the study show that Sealed Acid-Washed

Charcoal/Naltrexone that is not subject to tampering, *i.e.*, crushed, will not release a significant amount of naltrexone. The results also show that a sample of Sealed Acid-

- 10 Washed Charcoal/Naltrexone that is subject to tampering, *i.e.*, crushing followed by extraction with water or alcohol-containing solvent, will release naltrexone. The data in Table 2 further show that the extent of release from a crushed sample of Sealed Acid-Washed Charcoal/Naltrexone increases at elevated temperature. The results indicate that Sealed Acid-Washed Charcoal/Naltrexone is useful in a tamper resistant dosage form.

THE CLAIMS

What is claimed is:

1. A dosage form comprising an adsorbent and an adverse agent, wherein at least a majority of the adverse agent is adsorbed onto the adsorbent.
- 5 2. The dosage form of claim 1, wherein at least 80% of the adverse agent is adsorbed onto the adsorbent.
3. The dosage form of claim 2, wherein at least 90% of the adverse agent is adsorbed onto the adsorbent.
4. The dosage form of claim 1, wherein the adsorbent comprises at least one
10 material selected from the group consisting of activated charcoal, alumina, silicon dioxide bentonite, kaolin, and mixtures of any two or more of the foregoing.
5. The dosage form of claim 4, wherein the adsorbent is activated charcoal.
6. The dosage form of claim 1, further comprising at least one hydrophobic material disposed at least on a portion of the outer surface of the adsorbent.
- 15 7. The oral dosage form of claim 6, wherein the at least one hydrophobic material is selected from the group consisting of acrylic and methacrylic acid polymers and copolymers, alkylcelluloses, natural and synthetic waxes, water insoluble waxes, fatty alcohols, fatty acids, hydrogenated fats, fatty acid esters, fatty acid glycerides, hydrocarbons, and hydrophobic and hydrophilic polymers having hydrocarbon
20 backbones, and mixtures of any two or more of the foregoing.
8. The dosage form of claim 7, wherein the at least one hydrophobic material is selected from the group consisting of glyceryl monostearate; beeswax; cetyl alcohol; stearyl alcohol; hydrogenated castor oil; hydrogenated cottonseed; stearyl alcohol; stearic acid; and mixtures of any two or more of the foregoing.
- 25 9. The dosage form of claim 1, wherein the dosage form is an oral dosage form.

10. The dosage form of claim 1, wherein the dosage form releases about 0.5 mg or less of the adverse agent *in vivo* following intact administration.
11. The dosage form of claim 1, wherein the dosage form releases about 0.05 mg or less of the adverse agent *in vivo* following intact administration.
- 5 12. A dosage form comprising:
a plurality of first particles comprising an active agent; and
a plurality of second particles comprising an adsorbent and an adverse agent;
wherein
at least a majority of the adverse agent is adsorbed onto the adsorbent.
- 10 13. The dosage form of claim 12, wherein the adsorbent is selected from the group consisting of activated charcoal, alumina, bentonite, kaolin, and mixtures of any two or more of the foregoing.
14. The dosage form of claim 13, wherein the adsorbent is activated charcoal.
15. The dosage form of claim 12, wherein the plurality of second particles
15 further comprise at least one hydrophobic material disposed on at least a portion of the outer surface of the adsorbent.
16. The dosage form of claim 15, wherein the at least one hydrophobic material is selected from the group consisting of acrylic and methacrylic acid polymers and copolymers, alkylcelluloses, natural and synthetic waxes, water insoluble waxes,
20 fatty alcohols, fatty acids, hydrogenated fats, fatty acid esters, fatty acid glycerides, hydrocarbons, and hydrophobic and hydrophilic polymers having hydrocarbon backbones, and mixtures of any two or more of the foregoing.
17. The dosage form of claim 16, wherein the at least one hydrophobic material is selected from the group consisting of glyceryl monostearate; beeswax; cetyl
25 alcohol; stearyl alcohol; hydrogenated castor oil; hydrogenated cottonseed; stearyl alcohol; stearic acid; and mixtures of any two or more of the foregoing.
18. The dosage form of claim 12, wherein the active agent is an opioid agonist and the adverse agent is an opioid antagonist.

19. The dosage form of claim 18, wherein the opioid agonist is selected from the group consisting of alfentanil, allylprodine, alphaprodine, anileridine, benzylmorphine, bezitramide, buprenorphine, butorphanol, clonitazene, codeine, desomorphine, dextromoramide, dezocine, diampromide, dihydrocodeine, 5 dihydromorphine, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, eptazocine, ethoheptazine, ethylmethylthiambutene, ethylmorphine, etonitazene, fentanyl, heroin, hydrocodone, hydromorphone, hydroxypethidine, isomethadone, ketobemidone, levallorphan, levorphanol, levophenacyl morphan, lofentanil, meperidine, meptazinol, metazocine, methadone, metophon, morphine, 10 myrophine, nalbuphine, narceine, nicomorphine, norlevorphanol, normethadone, nalorphine, normorphine, norpipanone, opium, oxycodone, oxymorphone, papaveretum, pentazocine, phenadoxone, phenomorphan, phenazocine, phenoperidine, piminodine, piritramide, proheptazine, promedol, properidine, propiram, propoxyphene, sufentanil, tramadol, tilidine, pharmaceutically acceptable salts thereof, and mixtures of any two or 15 more of the foregoing.

20. The dosage form of claim 19, wherein the opioid agonist is selected from the group consisting of morphine, codeine, hydromorphone, hydrocodone, oxycodone, oxymorphone, dihydrocodeine, dihydromorphine, pharmaceutically acceptable salts thereof, and mixtures of any two or more of the foregoing.

21. The dosage form of claim 18, wherein the opioid antagonist is selected from the group consisting of cyclazocine, naloxone, naltrexone, nalmeferine, nalbuphine, 20 nalorphine, cyclazacine, levallorphan, pharmaceutically acceptable salts thereof, and mixtures of any two or more of the foregoing.

22. The dosage form of claim 21, wherein the opioid antagonist is selected 25 from the group consisting of nalmeferine, naloxone, naltrexone, pharmaceutically acceptable salts thereof, and mixtures of any two or more of the foregoing.

23. The dosage form of claim 12, wherein the dosage form is an oral dosage form.

24. The dosage form of claim 23, wherein the dosage form comprises a 30 capsule containing the first particles and the second particles.

25. The dosage form of claim 12, wherein the dosage form releases about 0.5 mg or less of the adverse agent *in vivo* following intact administration.
26. The dosage form of claim 25, wherein the dosage form releases about 0.05 mg or less of the adverse agent *in vivo* following intact administration.
- 5 27. An oral dosage form comprising:
a plurality of first particles comprising an opioid agonist;
a plurality of second particles comprising an adsorbent and an opioid
antagonist;
wherein at least a majority of the opioid agonist is adsorbed onto the
10 adsorbent; and
wherein the first particles provide a controlled release of the opioid
agonist upon oral administration to a patient.
28. The oral dosage form of claim 27, wherein the first particles and the
15 second particles each have a size ranging from about 0.1 mm to about 3.0 mm in any
dimension.
29. The oral dosage form of claim 27, wherein the second particles each
comprise at least one hydrophobic material disposed on at least a portion of the outer
surface of the adsorbent.
- 20 30. The oral dosage form of claim 29, wherein the at least one hydrophobic
material is selected from the group consisting of acrylic and methacrylic acid polymers
and copolymers, alkylcelluloses, natural and synthetic waxes, water insoluble waxes,
fatty alcohols, fatty acids, hydrogenated fats, fatty acid esters, fatty acid glycerides,
hydrocarbons, and hydrophobic and hydrophilic polymers having hydrocarbon
25 backbones, and mixtures of any two or more of the foregoing.
31. The oral dosage form of claim 30, wherein the at least one hydrophobic
material is selected from the group consisting of glyceryl monostearate; beeswax; cetyl
alcohol; stearyl alcohol; hydrogenated castor oil; hydrogenated cottonseed; stearyl
alcohol; stearic acid; and mixtures of any two or more of the foregoing.

32. The oral dosage form of claim 27, wherein the opioid agonist is selected from the group consisting of alfentanil, allylprodine, alphaprodine, anileridine, benzylmorphine, bezitramide, buprenorphine, butorphanol, clonitazene, codeine, desomorphine, dextromoramide, dezocine, diampromide, dihydrocodeine,
- 5 dihydromorphine, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, eptazocine, ethoheptazine, ethylmethylthiambutene, ethylmorphine, etonitazene, fentanyl, heroin, hydrocodone, hydromorphone, hydroxypethidine, isomethadone, ketobemidone, levallorphan, levorphanol, levophenacyl morphan, lofentanil, meperidine, meptazinol, metazocine, methadone, metophon, morphine,
- 10 myrophine, nalbuphine, narceine, nicomorphine, norlevorphanol, normethadone, nalorphine, normorphine, norpipanone, opium, oxycodone, oxymorphone, papaveretum, pentazocine, phenadoxone, phenomorphan, phenazocine, phenoperidine, piminodine, piritramide, proheptazine, promedol, properidine, propiram, propoxyphene, sufentanil, tramadol, tilidine, pharmaceutically acceptable salts thereof, and mixtures of any two or
- 15 more of the foregoing.

33. The oral dosage form of claim 32, wherein the opioid agonist is selected from the group consisting of morphine, codeine, hydromorphone, hydrocodone, oxycodone, oxymorphone, dihydrocodeine, dihydromorphine, pharmaceutically acceptable salts thereof, and mixtures of any two or more of the foregoing.

- 20 34. The oral dosage form of claim 27, wherein the opioid antagonist is selected from the group consisting of cyclazocine, naloxone, naltrexone, nalmeferine, nalbuphine, nalorphine, cyclazacine, levallorphan, pharmaceutically acceptable salts thereof, and mixtures of any two or more of the foregoing.

35. The oral dosage form of claim 34, wherein the opioid antagonist is
- 25 selected from the group consisting of naloxone, naltrexone and nalmeferine, pharmaceutically acceptable salts thereof, any mixtures of any two or more of the foregoing.

36. The oral dosage form of claim 27, wherein the dosage form comprises a tablet comprising the first particles and the second particles.

- 30 37. The oral dosage form of claim 27, wherein the dosage form comprises a capsule containing the first particles and the second particles.

38. The oral dosage form of claim 27, wherein the second particles release about 0.5 mg or less of the opioid antagonist *in vivo* following intact oral administration.
39. The oral dosage form of claim 38, wherein the second particles release about 0.05 mg or less of the opioid antagonist *in vivo* following intact oral
5 administration.
40. A dosage form comprising
an active agent;
an adsorbent; and
an adverse agent; wherein at least a majority of the adverse agent is
10 adsorbed onto the adsorbent.
41. The dosage form of claim 40, further comprising at least one hydrophobic material disposed on at least a portion of the outer surface of the adsorbent.
42. The oral dosage form of claim 41, wherein the at least one hydrophobic material is selected from the group consisting of acrylic and methacrylic acid polymers
15 and copolymers, alkylcelluloses, natural and synthetic waxes, water insoluble waxes, fatty alcohols, fatty acids, hydrogenated fats, fatty acid esters, fatty acid glycerides, hydrocarbons, and hydrophobic and hydrophilic polymers having hydrocarbon backbones, and mixtures of any two or more of the foregoing.
43. The dosage form of claim 42, wherein the at least one hydrophobic
20 material is selected from the group consisting of glyceryl monostearate; beeswax; cetyl alcohol; stearyl alcohol; hydrogenated castor oil; hydrogenated cottonseed; stearyl alcohol; stearic acid; and mixtures of any two or more of the foregoing. and mixtures of any two or more of the foregoing.
44. The dosage form of claim 40, wherein the active agent is an opioid agonist
25 and the adverse agent is an opioid antagonist.
45. The dosage form of claim 44, wherein the opioid agonist is selected from the group consisting of alfentanil, allylprodine, alphaprodine, anileridine, benzylmorphine, bezitramide, buprenorphine, butorphanol, clonitazene, codeine, desomorphine, dextromoramide, dezocine, diampromide, dihydrocodeine,
30 dihydromorphine, dimenoxadol, dimепheptanol, dimethylthiambutene, dioxaphetyl

butyrate, dipipanone, eptazocine, ethoheptazine, ethylmethylthiambutene, ethylmorphine, etonitazene, fentanyl, heroin, hydrocodone, hydromorphone, hydroxypethidine, isomethadone, ketobemidone, levallorphan, levorphanol, levophenacyl morphan, lofentanil, meperidine, meptazinol, metazocine, methadone, metopon, morphine, 5 myrophine, nalbuphine, narceine, nicomorphine, norlevorphanol, normethadone, nalorphine, normorphine, norpipanone, opium, oxycodone, oxymorphone, papaveretum, pentazocine, phenadoxone, phenomorphan, phenazocine, phenoperidine, piminodine, piritramide, proheptazine, promedol, properidine, propiram, propoxyphene, sufentanil, tramadol, tilidine, pharmaceutically acceptable salts thereof, and mixtures of any two or 10 more of the foregoing.

46. The dosage form of claim 45, wherein the opioid agonist is selected from the group consisting of morphine, codeine, hydromorphone, hydrocodone, oxycodone, oxymorphone, dihydrocodeine, dihydromorphine, pharmaceutically acceptable salts thereof, and mixtures of any two or more of the foregoing.

15 47. The dosage form of claim 44, wherein the opioid antagonist is selected from the group consisting of cyclazocine, naloxone, naltrexone, nalmeferine, nalbuphine, nalorphine, cyclazacine, levallorphan, pharmaceutically acceptable salts thereof, and mixtures of any two or more of the foregoing.

20 48. The dosage form of claim 47, wherein the opioid antagonist is selected from the group consisting of nalmeferine, naloxone, naltrexone, pharmaceutically acceptable salts thereof, and mixtures of any two or more of the foregoing.

49. The dosage form of claim 44, wherein the dosage form is an oral dosage form.

25 50. The dosage form of claim 44, wherein the dosage form comprises a capsule containing a plurality of particles.

51. The dosage form of claim 44, wherein the dosage form comprises a tablet.

52. The dosage form of claim 40, wherein the adsorbent comprises at least one material selected from the group consisting of activated charcoal, alumina, bentonite, kaolin, and mixtures of any two or more of the foregoing.

53. The dosage form of claim 52, wherein the adsorbent is activated charcoal.
54. The oral dosage form of claim 40, wherein the dosage form releases about 0.5 mg or less of the adverse agent *in vivo* following intact oral administration.
55. The oral dosage form of claim 54, wherein the dosage form releases about 0.05 mg or less of the adverse agent *in vivo* following intact oral administration.
56. The dosage form of claim 40, wherein the dosage form further comprises:
a core comprising the adsorbent and the adverse agent; and
a shell comprising the active agent;
wherein the shell surrounds a majority of the core.
57. A method for preparing a dosage form comprising:
providing an adsorbent;
providing a liquid comprising an adverse agent;
contacting the adsorbent with the liquid comprising the adverse agent for sufficient time to allow at least a portion of the adverse agent to adsorb onto the adsorbent;
separating the adsorbent from the liquid phase; and
optionally, washing the adsorbent.
58. The method of claim 57, wherein the adsorbent comprises at least one material selected from the group consisting of activated charcoal, alumina, bentonite, kaolin, and mixtures of and two or more of the foregoing.
59. The method of claim 57, further comprising applying at least one hydrophobic material to the outer surface of the adsorbent after removal of the adsorbent from the liquid phase.
60. The method of claim 59, wherein the at least one hydrophobic material is selected from the group consisting of acrylic and methacrylic acid polymers and copolymers, alkylcelluloses, natural and synthetic waxes, water insoluble waxes, fatty alcohols, fatty acids, hydrogenated fats, fatty acid esters, fatty acid glycerides, hydrocarbons, and hydrophobic and hydrophilic polymers having hydrocarbon backbones, and mixtures of any two or more of the foregoing.

61. The method of claim 57, wherein the adverse agent is an opioid antagonist.
62. The method of claim 61, further comprising adding the adsorbent and an opioid agonist to a dosage form.
- 5 63. A method for preparing a dosage form comprising:
providing an adsorbent;
providing a liquid comprising an adverse agent;
adding the adsorbent to a fluidized bed;
fluidizing the adsorbent;
10 spraying the liquid onto the fluidized adsorbent; and
optionally, drying the adsorbent.
64. The method of claim 63, wherein the adsorbent comprises at least one material selected from the group consisting of activated charcoal, alumina, bentonite, kaolin, and mixtures of and two or more of the foregoing.
- 15 65. The method of claim 63, further comprising applying at least one hydrophobic material to the outer surface of the adsorbent after removal of the adsorbent from the liquid phase.
66. The method of claim 65, wherein the at least one hydrophobic material is selected from the group consisting of acrylic and methacrylic acid polymers and
20 copolymers, alkylcelluloses, natural and synthetic waxes, water insoluble waxes, fatty alcohols, fatty acids, hydrogenated fats, fatty acid esters, fatty acid glycerides, hydrocarbons, and hydrophobic and hydrophilic polymers having hydrocarbon backbones, and mixtures of any two or more of the foregoing.
67. The method of claim 63, wherein the adverse agent is an opioid
25 antagonist.
68. The method of claim 63, further comprising adding the adsorbent and an opioid agonist to a dosage form.
69. A method of treating a condition, or a symptom thereof, in a patient comprising administering to the patient a dosage form according to claim 40.

70. A method of treating a patient for pain comprising administering to the patient a dosage form according to claim 27.

71. A kit for treating a patient for pain comprising a dosage form according to claim 27, and instructions for directing the administration of the dosage form to the
5 patient for the treatment of pain.

ABSTRACT

Pharmaceutical compositions and dosage forms comprising an adsorbent, and an adverse agent, such as an opioid antagonist. In one embodiment, at least a portion of the adverse agent is on the surface or within the micropore structure of an adsorbent material. The pharmaceutical compositions and dosage forms comprising the adsorbent and the adverse agent are useful for preventing or discouraging tampering, abuse, misuse or diversion of a dosage form containing an active pharmaceutical agent, such as an opioid. The present invention also relates to methods for treating a patient with such a dosage form, as well as kits containing such a dosage form with instructions for using the dosage form to treat a patient. The present invention further relates to process for preparing such pharmaceutical compositions and dosage forms.

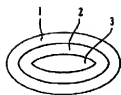


Fig. 1a

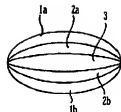


Fig. 1b

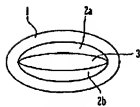


Fig. 1c

FIG. 1

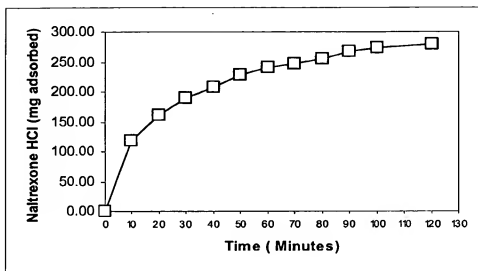


FIG. 2

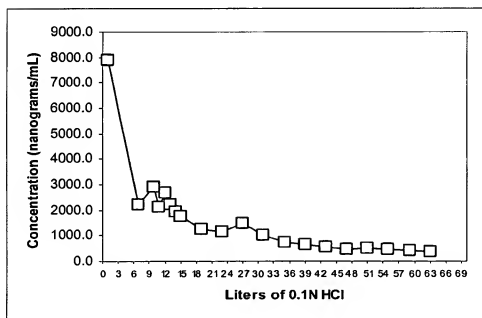


FIG. 3

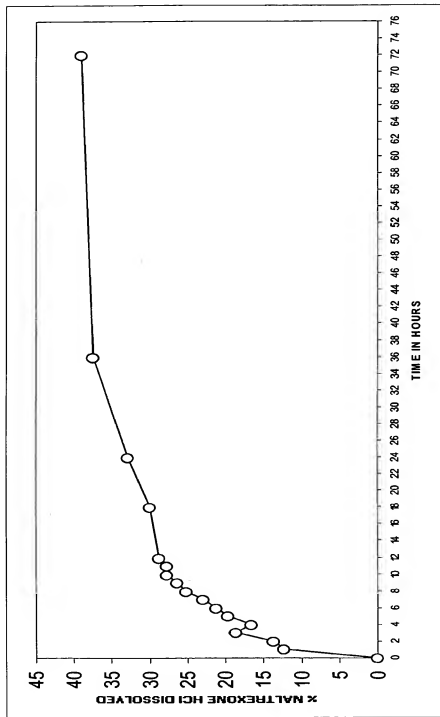


FIG. 4

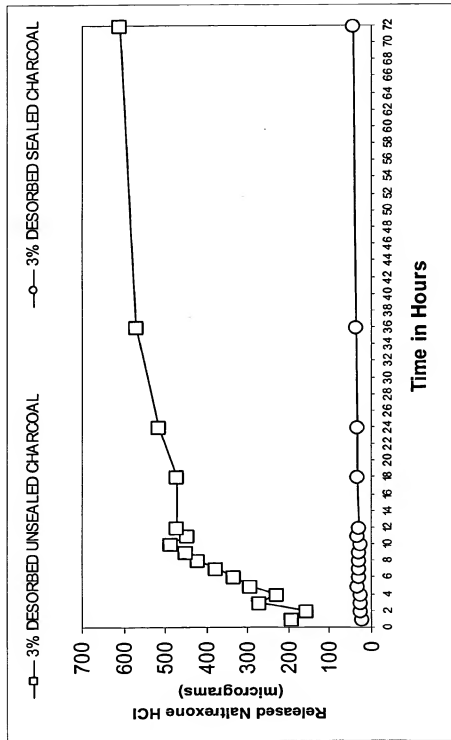


FIG. 5